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(54) Benzamide derivatives, useful as cell differentiation inducers

Benzamid-Derivate, verwendbar als Zelldifferenzierungsinduktion

Dérivés de benzamide, utiles comme inducteurs de différentiation cellulaire

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- **CHEMICAL ABSTRACTS, vol. 119, no. 25, 20 December 1993 Columbus, Ohio, US; abstract no. 270986n, J. NOWAKOWSKI: "Method for preparation of novel N-phenylcarbamoyl derivatives of difurylethane and difuryldichloroethylene." page 978; XP002051610 & PL 157 443 B (UNIWERSYTET MIKOLAJA KOPERNIKA)**
- **Y. V. MITIN ET AL.: "Rearrangement of ortho-O-aminoacyl,N-acylaminophenol." TETRAHEDRON LETTERS., no. 12, 1979, OXFORD GB, pages 1081-1084, XP002051608**

EP 0 847 992 B1

Description

[0001] This invention relates to a differentiation-inducing agent. In particular, this invention relates to a pharmaceutical composition comprising a specific type of benzamide derivative, particularly for an anticancer drug or other drugs based on its differentiation-inducing activity.

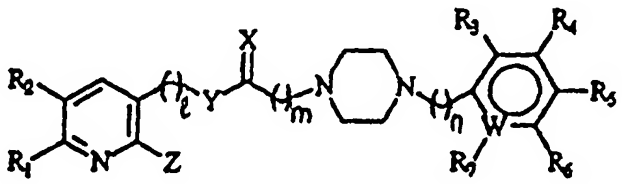
[0002] Cancers have now become a top cause of death, exceeding heart and cerebrovascular diseases, and so many studies have been conducted with enormous expense and time to overcome cancers. They have not been, however, overcome in spite of a variety of investigations for therapy such as a surgical operation, a radiation therapy and thermotherapy. Among those therapies, chemotherapy is one of the main area for cancer treatment. To date, however, no satisfactory drugs have been discovered, and thus an anticancer drug with reduced toxicity and high therapeutic effect has been desired. Many of the conventional anticancer drugs show their effect by affecting mainly DNA to express their cytotoxicity and then injuring carcinoma cells. However, since they do not have sufficient selectivity between carcinoma cells and normal cells, adverse reactions expressed in normal cells have limited their use in therapy.

[0003] Meanwhile, differentiation-inducing agents among anticancer drugs are intended to induce differentiation of carcinoma cells for controlling their infinite proliferation, rather than directly kill the cells.

[0004] The agents may, therefore, be inferior to the anticancer drugs directly killing carcinoma cells, with regard to involution of a carcinoma, but may be expected to have reduced toxicity and different selectivity. In fact, it is well known that retinoic acid, a differentiation-inducing agent, may be used for treatment of acute promyelogenous leukemia to exhibit a higher effect [Huang et al., Blood, 72, 567-572 (1988); Castaign et al., Blood, 76, 1704-1709 (1990); Warrell et al., NewEngl.J.Med. 324, 1385-1393(1991) etc.]. In addition, vitamin D derivatives exhibit differentiation-inducing effect, and thus their application for anticancer drugs have been investigated [e.g., Olsson et al, Cancer Res. 43, 5862-5867(1983) etc.].

[0005] As the results of these investigations, there have been reported applications for anticancer drugs, of a variety of differentiation-inducing agents such as vitamin D derivatives (JP-A 6-179622), isoprene derivatives (JP-A6-192073), tocopherol (JP-A6-256181), quinone derivatives (JP-A 6-305955), noncyclic polyisoprenoids (JP-A 6-316520), benzoic acid derivatives (JP-A 7-206765) and glycolipids (JP-A 7-258100). There have been no agents having sufficient level of effect for cancer treatment in spite of the investigations, and thus there has been greatly desired a highly safe agent effective to a variety of cancers.

[0006] WO 96/21648 relates to antitumour compositions based on piperazines (I):

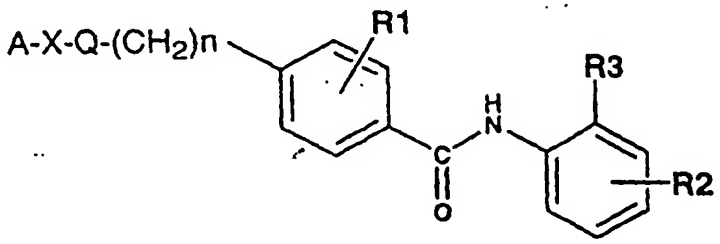


(I)

[0007] Preferred embodiments of this invention may provide compounds which exhibit differentiation-inducing effects and are useful as pharmaceutical agents such as therapeutic or improving agents for malignant tumors, autoimmune diseases, dermatologic diseases and parasitism.

[0008] We have intensely researched and have found that a novel benzamide derivative having differentiation-inducing effect shows antitumor effect.

[0009] This invention provides a compound represented by formula (1) or a pharmaceutically acceptable salt thereof:

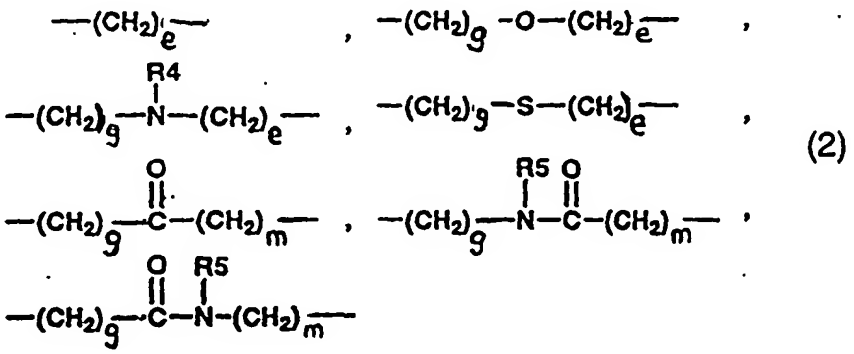


(1)

wherein A is a phenyl or heterocyclic group, optionally substituted with 1 to 4 substituents selected from the group consisting of a halogen atom, a hydroxyl group, an amino group, a nitro group, a cyano group, an alkyl group having 1 to 4 carbons, an alkoxy group having 1 to 4 carbons, an aminoalkyl group having 1 to 4 carbons, an alkylamino group

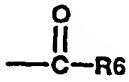
having 1 to 4 carbons, an acyl group having 1 to 4 carbons, an acylamino group having 1 to 4 carbons, an alkylthio group having 1 to 4 carbons, a perfluoroalkyl group having 1 to 4 carbons, a perfluoroalkyloxy group having 1 to 4 carbons, a carboxyl group, an alkoxycarbonyl group having 1 to 4 carbons, a phenyl group and a heterocyclic group;

X is a bond or a moiety having a structure selected from those illustrated in formula (2)



(2)

wherein e is an integer of 1 to 4; g and m are independently an integer of 0 to 4; R^4 is hydrogen or an optionally substituted alkyl group having 1 to 4 carbons, or the acyl group represented by formula (3)

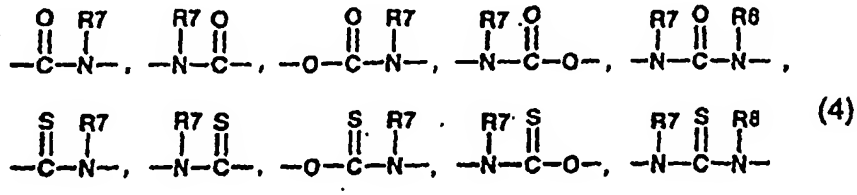


(3)

wherein R^6 is an optionally substituted alkyl group having 1 to 4 carbons, a perfluoroalkyl group having 1 to 4 carbons, a phenyl group or a heterocyclic group; R^5 is hydrogen or an optionally substituted alkyl group having 1 to 4 carbons;

n is an integer of 0 to 4, provided that when X is a bond, n is not zero;

Q is a moiety having a structure selected from those illustrated in formula (4)



(4)

wherein R^7 and R^8 are independently hydrogen or an optionally substituted alkyl having 1 to 4 carbons;

R^1 and R^2 are independently a hydrogen atom, a halogen atom, a hydroxyl group, amino group, an alkyl group having 1 to 4 carbons, an alkoxy group having 1 to 4 carbons, an aminoalkyl group having 1 to 4 carbons, an alkylamino group having 1 to 4 carbons, an acyl group having 1 to 4 carbons, an acylamino group having 1 to 4 carbons, an alkylthio group having 1 to 4 carbons, a perfluoroalkyl group having 1 to 4 carbons, a perfluoroalkyloxy group having 1 to 4 carbons, a carboxyl group or an alkoxycarbonyl group having 1 to 4 carbons;

R^3 is an amino group.

[0010] WO-A-97/24328 discloses a range of compounds which would overlap with the compounds of formula (1) were it not for the requirement that R^3 is an amino group. The compounds, in which R^3 is OH, are said to be useful for treatment of respiratory diseases and inflammatory processes.

[0011] Preferred benzamide derivatives used in this invention have differentiation-inducing effect and are useful as a drug such as a therapeutic or improving agent for malignant tumors, autoimmune diseases, dermatologic diseases and parasitism. In particular, they are highly effective as a carcinostatic agent, specifically to a hematologic malignancy and a solid carcinoma.

[0012] In further aspects the invention provides: (a) an anticancer drug comprising one or more compounds of formula (1);

(b) use of a compound of formula (1) in the manufacture of a composition for use in the treatment of cancer;

(c) a compound represented by formula (1) or a pharmaceutically acceptable salt thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

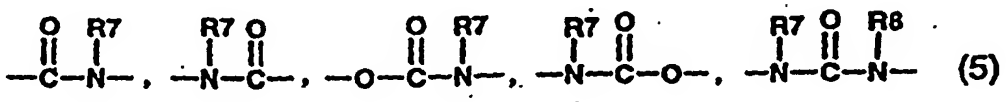
[0013]

Figure 1 shows a change of the volume of the tumour when the compound of Example 44 was administered against the tumour cell HT-29.
Figure 2 shows a change of the volume of the tumour when the compound of Example 44 was administered against the tumor cell KB-3-1.

DETAILED DESCRIPTION OF THE INVENTION AND PREFERRED EMBODIMENTS

[0014] In the above formula (1), n may be zero or an integer of 1 to 4.

[0015] Q in the above formula (1) may be any structure illustrated in formula (5);



(5)

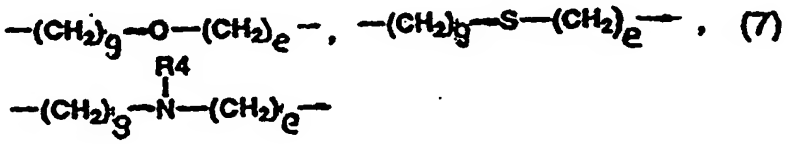
wherein R^7 and R^8 are as defined above.

[0016] X in the above formula (1) may be a moiety having the structure represented by formula (6);

$$-(CH_2)e- \quad (6)$$

wherein e is as defined above.

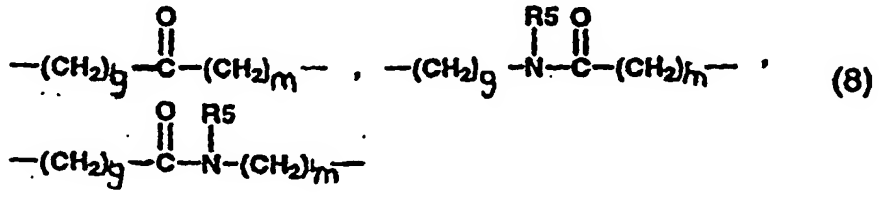
[0017] X in the above formula (1) may be also a moiety having any structure illustrated in formula (7);



(7)

wherein e, g and R^4 are as defined above.

[0018] X in the above formula (1) may be also a moiety having any structure illustrated in formula (8),



(8)

wherein g, m and R^5 are as defined above.

[0019] As used herein, "1 to 4 carbons" means a carbon number per a single substituent; for example, for dialkyl substitution it means 2 to 8 carbons.

[0020] A heterocycle in the compound represented by formula (1) may be a monocyclic heterocycle having 5 or 6 members containing 1 to 4 nitrogen, oxygen or sulfur atoms or a bicyclic-fused heterocycle. The monocyclic heterocycle

includes pyridine, pyrazine, pyrimidine, pyridazine, thiophene, furan, pyrrole, pyrazole, isoxazole, isothiazole, imidazole, oxazole, thiazole, piperidine, piperazine, pyrrolidine, quinuclidine, tetrahydrofuran, morpholine, thiomorpholine and the like. The bicyclic fused heterocycle includes quinoline; isoquinoline; naphthyridine; fused pyridines such as furopyridine, thienopyridine, pyrrolopyridine, oxazolopyridine, imidazolopyridine and thiazolopyridine; benzofuran; benzothiophene; benzimidazole and the like.

[0021] A halogen may be fluorine, chlorine, bromine or iodine.

[0022] An alkyl having 1 to 4 carbons includes methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl and tert-butyl.

[0023] An alkoxy having 1 to 4 carbons includes methoxy, ethoxy, n-propoxy, isopropoxy, allyloxy, n-butoxy, isobutoxy, sec-butoxy, tert-butoxy and the like.

[0024] An aminoalkyl having 1 to 4 carbons includes aminomethyl, 1-aminoethyl, 2-aminopropyl and the like.

[0025] An alkylamino having 1 to 4 carbons includes N-methylamino, N,N-dimethylamino, N,N-diethylamino, N-methyl-N-ethylamino, N,N-diisopropylamino and the like.

[0026] An acyl having 1 to 4 carbons includes acetyl, propanoyl, butanoyl and like.

[0027] An acylamino having 1 to 4 carbons includes acetylamino, propanoylamino, butanoylamino and the like.

[0028] An alkylthio having 1 to 4 carbons includes methylthio, ethylthio, propylthio and the like.

[0029] A perfluoroalkyl having 1 to 4 carbons includes trifluoromethyl, pentafluoroethyl and the like.

[0030] A perfluoroalkyloxy having 1 to 4 carbons includes trifluoromethoxy, pentafluoroethoxy and the like.

[0031] An alkoxycarbonyl having 1 to 4 carbons includes methoxycarbonyl and ethoxycarbonyl.

[0032] An optionally substituted alkyl having 1 to 4 carbons includes methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl and tert-butyl and these having 1 to 4 substituents selected from the group consisting of a halogen, hydroxyl, amino, nitro, cyano, phenyl and a heterocycle.

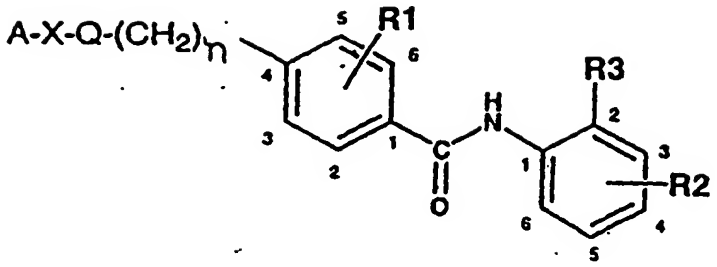
[0033] A pharmaceutically acceptable salt of the compound of this invention includes salts with an inorganic acid such as hydrochloric acid, hydrobromic acid, sulfuric acid and phosphoric acid; and with an organic acid such as acetic acid, lactic acid, tartaric acid, malic acid, succinic acid, fumaric acid, maleic acid, citric acid, benzoic acid, trifluroacetic acid, p-toluenesulfonic acid and methanesulfonic acid. Such a salt includes N-(2-aminophenyl)-4-[N-(pyridin-3-yl)methoxycarbonylaminomethyl]benzamide hydrochloride, N-(2-aminophenyl)-4-[N-(pyridin-3-yl)methoxycarbonylaminomethyl]benzamide hydrobromide, N-(2-aminophenyl)-4-[N-(pyridin-3-yl)methoxycarbonylaminomethyl]benzamide sulfate, N-(2-aminophenyl)-4-[N-(pyridin-3-yl)methoxycarbonylaminomethyl]benzamide phosphate, N-(2-aminophenyl)-4-[N-(pyridin-3-yl)methoxycarbonylaminomethyl]benzamide acetate, N-(2-aminophenyl)-4-[N-(pyridin-3-yl)methoxycarbonylaminomethyl]benzamide lactate, N-(2-aminophenyl)-4-[N-(pyridin-3-yl)methoxycarbonylaminomethyl]benzamide tartrate, N-(2-aminophenyl)-4-[N-(pyridin-3-yl)methoxycarbonylaminomethyl]benzamide malate, N-(2-aminophenyl)-4-[N-(pyridin-3-yl)methoxycarbonylaminomethyl]benzamide succinate, , N-(2-aminophenyl)-4-[N-(pyridin-3-yl)methoxycarbonylaminomethyl]benzamide fumarate, N-(2-aminophenyl)-4-[N-(pyridin-3-yl)methoxycarbonylaminomethyl]benzamide maleate, N-(2-aminophenyl)-4-[N-(pyridin-3-yl)methoxycarbonylaminomethyl]benzamide citrate, N-(2-aminophenyl)-4-[N-(pyridin-3-yl)methoxycarbonylaminomethyl]benzamide trifluoroacetate, N-(2-aminophenyl)-4-[N-(pyridin-3-yl)methoxycarbonylaminomethyl]benzamide p-toluenesulfonate and N-(2-aminophenyl)-4-[N-(pyridin-3-yl)methoxycarbonylaminomethyl]benzamide methanesulfonate.

[0034] As used herein, a "drug" includes a therapeutic and/or improving agent to, for example, an autoimmune disease, dermatologic disease or parasitism, in addition to a anticancer drug.

[0035] When having asymmetric carbon or carbons, the compound represented by formula (1) may be obtained as an individual stereoisomer or a mixture of stereoisomers including a racemic modification. This invention encompasses the above-specified different forms, which may be also used as an active ingredient.

[0036] Representative compounds of this invention represented by formula (1) are specifically shown in Table 1, but this invention is not intended to be limited to these.

Table 1 (1)



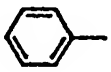
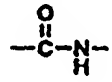
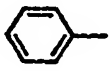
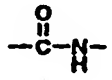
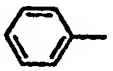
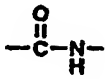
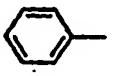
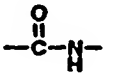
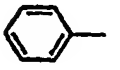
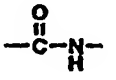
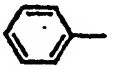
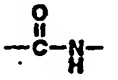
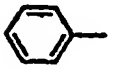
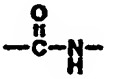
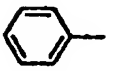
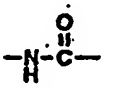
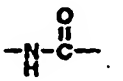
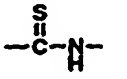
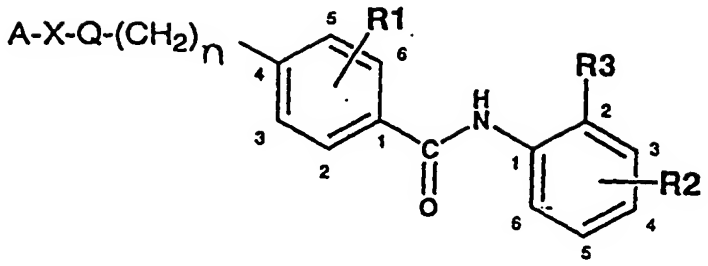
Compound No.	A	X	Q	n	R1	R2	R3
1		Direct bond		1	H	H	NH_2
2		$-CH_2-$		0	H	H	NH_2
3		$-(CH_2)_2-$		0	H	H	NH_2
4		$-(CH_2)_3-$		0	H	H	NH_2
5		$-(CH_2)_4-$		0	H	H	NH_2
6		$-CH_2-$		1	H	H	NH_2
7		$-(CH_2)_2-$		1	H	H	NH_2
8		$-CH_2-$		0	H	H	NH_2
9		$-(CH_2)_2-$		0	H	H	NH_2
10		Direct bond		1	H	H	NH_2

Table 1 (2)



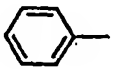
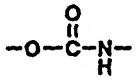
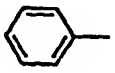
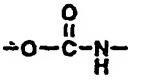
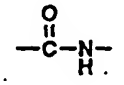
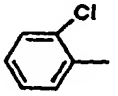
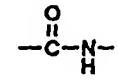
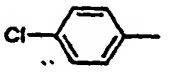
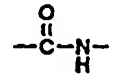
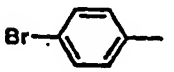
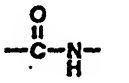
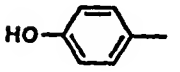
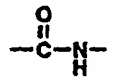
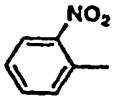
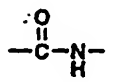
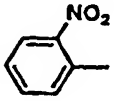
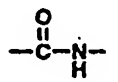
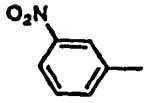
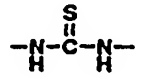
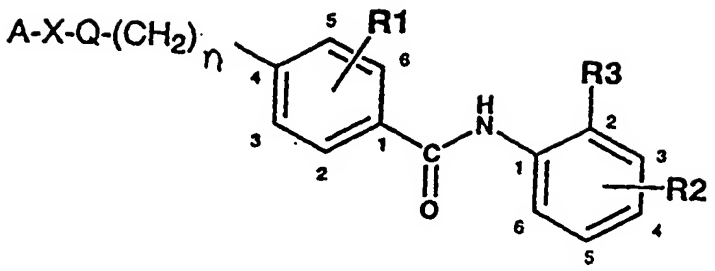
Compound No.	A	X	Q	n	R1	R2	R3
1 1		-CH_2-		1	H	H	NH_2
1 2		Direct bond		1	H	H	NH_2
1 3		Direct bond		1	H	H	NH_2
1 4		Direct bond		1	H	H	NH_2
1 5		-CH_2-		0	H	H	NH_2
1 6		Direct bond		1	H	H	NH_2
1 7		Direct bond		1	H	H	NH_2
1 8		Direct bond		1	H	H	NH_2
1 9		-CH_2-		0	H	H	NH_2
2 0		Direct bond		1	H	H	NH_2

Table 1 (3)



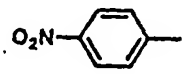
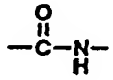
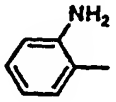
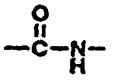
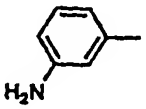
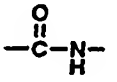
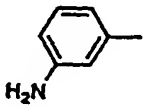
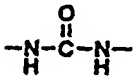
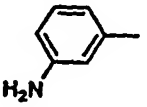
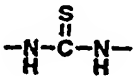
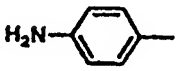
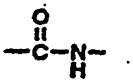
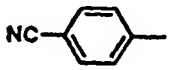
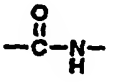
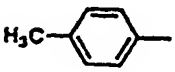
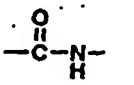
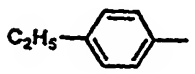
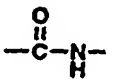
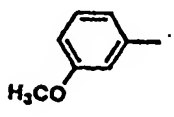
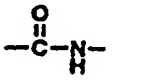
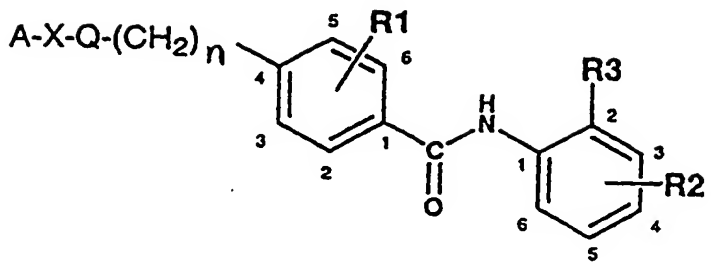
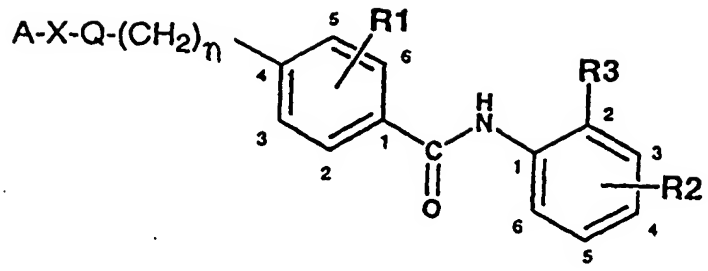
Compound No.	A	X	Q	n	R1	R2	R3
21		-CH2-		0	H	H	NH2
22		-CH2-		0	H	H	NH2
23		-CH2-		1	H	H	NH2
24		Direct bond		1	H	H	NH2
25		Direct bond		1	H	H	NH2
26		-CH2-		0	H	H	NH2
27		Direct bond		1	H	H	NH2
28		Direct bond		1	H	H	NH2
29		Direct bond		1	H	H	NH2
30		Direct bond		1	H	H	NH2

Table 1 (4)



Compound No.	A	X	Q	n	R1	R2	R3
31	H_3CO–	Direct bond	–C(=O)–N(H)–	1	H	H	NH_2
32	H_3CO–	$-CH_2-$	–C(=O)–N(H)–	0	H	H	NH_2
33	3,4,5-trimethoxy	Direct bond	–C(=O)–N(H)–	1	H	H	NH_2
34	3,4,5-trimethoxy	$-CH_2-$	–O–C(=O)–N(H)–	1	H	H	NH_2
35	H_3CHN–	Direct bond	–C(=O)–N(H)–	1	H	H	NH_2
36	$(H_3C)_2N$–	Direct bond	–C(=O)–N(H)–	1	H	H	NH_2
37	H_2N–	Direct bond	–N(H)–C(=O)–N(H)–	1	H	H	NH_2
38	H_3CHN–C(=O)–	$-CH_2-$	–O–C(=O)–N(H)–	1	H	H	NH_2
39	H_3C–C(=O)–N(H)–	$-CH_2-$	–O–C(=O)–N(H)–	1	H	H	NH_2
40	H_3C–C(=O)–	Direct bond	–C(=O)–N(H)–	1	H	H	NH_2

Table 1 (5)



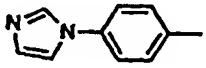
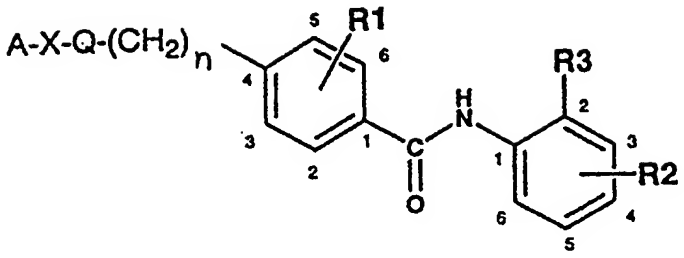
Compound No.	A	X	Q	n	R1	R2	R3
41	H_3CS-Ph-	Direct bond	-C(=O)-NH-	1	H	H	NH_2
42	F_3C-Ph-	Direct bond	-C(=O)-NH-	1	H	H	NH_2
43	F_3C-Ph-	$-CH_2-$	-C(=O)-NH-	0	H	H	NH_2
44	F_3CO-Ph-	Direct bond	-C(=O)-NH-	1	H	H	NH_2
45	HO_2C-Ph-	Direct bond	-C(=O)-NH-	1	H	H	NH_2
46	H_3CO_2C-Ph-	Direct bond	-C(=O)-NH-	1	H	H	NH_2
47		$-CH_2-$	-O-C(=O)-NH-	1	H	H	NH_2
48	Ph-	$-O-CH_2-$	-C(=O)-NH-	1	H	H	NH_2
49	Ph-	$-S-CH_2-$	-C(=O)-NH-	1	H	H	NH_2
50	Ph-	$-NH-CH_2-$	-C(=O)-NH-	1	H	H	NH_2

Table 1 (6)



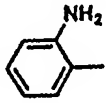
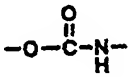
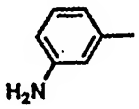
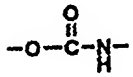
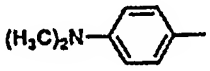
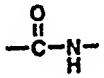
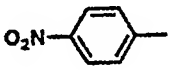
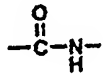
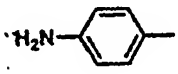
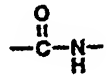
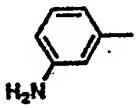
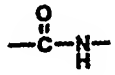
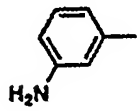
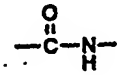
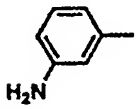
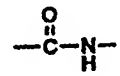
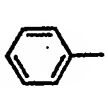
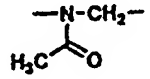
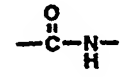
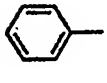
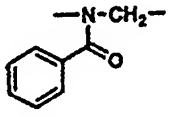
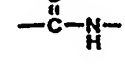
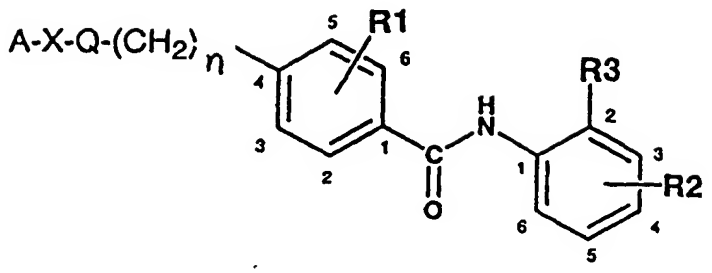
Compound No.	A	X	Q	n	R1	R2	R3
5 1		-CH2-		1	H	H	NH2
5 2		-CH2-		1	H	H	NH2
5 3		—CH2—		0	H	H	NH2
5 4		—O-CH2—		0	H	H	NH2
5 5		—O-CH2—		0	H	H	NH2
5 6		—O-CH2—		1	H	H	NH2
5 7		—O-CH2—		1	H	5-F	NH2
5 8		—CH2-O-CH2—		0	H	H	NH2
5 9				1	H	H	NH2
6 0				1	H	H	NH2

Table 1 (7)



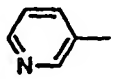
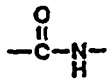
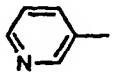
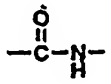
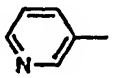
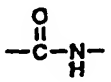
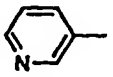
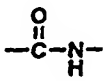
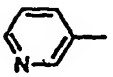
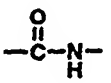
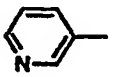
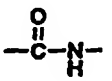
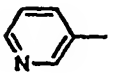
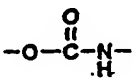
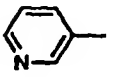
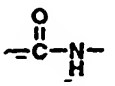
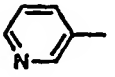
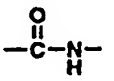
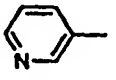
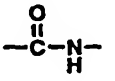
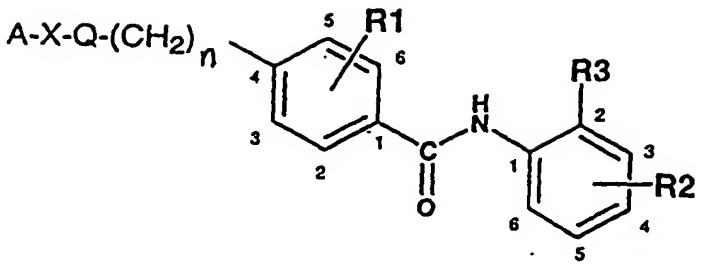
Compound No.	A	X	Q	n	R1	R2	R3
6 1		$-O-CH_2-$		1	H	H	NH_2
6 2		$-O-(CH_2)_2-$		1	H	H	NH_2
6 3		$-\underset{H}{N}-CH_2-$		1	H	H	NH_2
6 4		$-S-CH_2-$		1	H	H	NH_2
6 5		$-O-CH_2-$		0	H	H	NH_2
6 6		$-O-(CH_2)_2-$		0	H	H	NH_2
6 7		$-O-(CH_2)_2-$		0	H	H	NH_2
6 8		$-CH_2-$		0	H	H	NH_2
6 9		$-(CH_2)_2-$		0	H	H	NH_2
7 0		$-(CH_2)_3-$		0	H	H	NH_2

Table 1 (8)



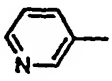
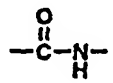
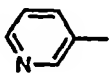
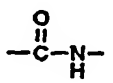
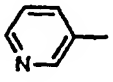
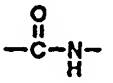
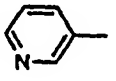
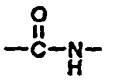
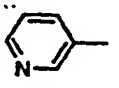
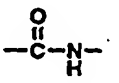
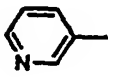
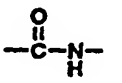
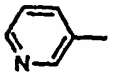
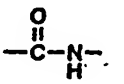
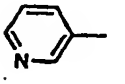
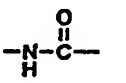
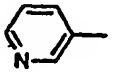
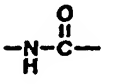
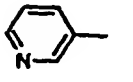
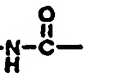
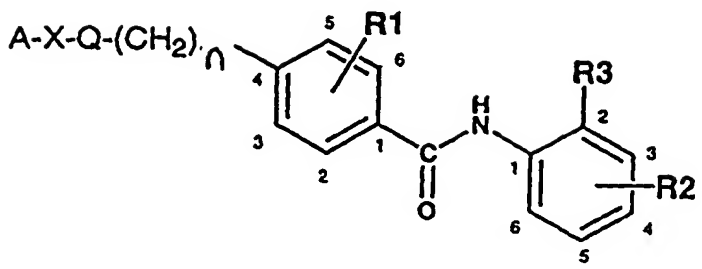
Compound No.	A	X	Q	n	R1	R2	R3
71		Direct bond		1	H	H	NH_2
72		Direct bond		2	H	H	NH_2
73		Direct bond		3	H	H	NH_2
74		$-CH_2-$		1	H	H	NH_2
75		$-(CH_2)_2-$		1	H	H	NH_2
76		$-(CH_2)_3-$		1	H	H	NH_2
77		$-CH_2-$		2	H	H	NH_2
78		$-CH_2-$		1	H	H	NH_2
79		Direct bond		2	H	H	NH_2
80		$-CH_2-$		2	H	H	NH_2

Table 1 (9)



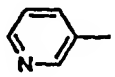
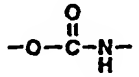
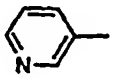
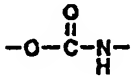
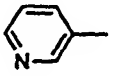
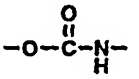
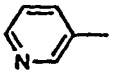
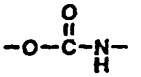
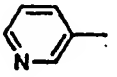
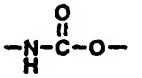
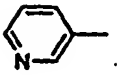
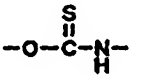
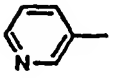
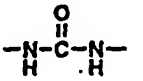
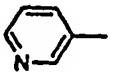
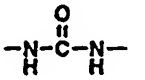
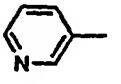
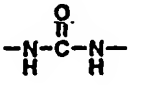
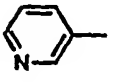
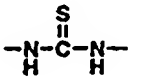
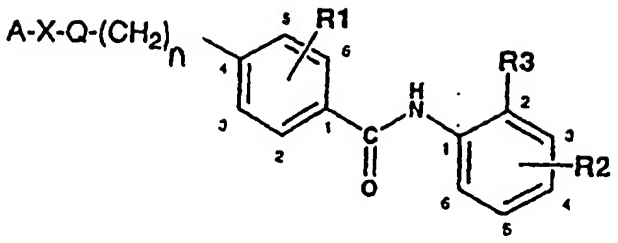
Compound No.	A	X	Q	n	R1	R2	R3
81		Direct bond		1	H	H	NH_2
82		$-CH_2-$		1	H	H	NH_2
83		$-(CH_2)_2-$		1	H	H	NH_2
84		$-(CH_2)_3-$		1	H	H	NH_2
85		$-CH_2-$		1	H	H	NH_2
86		$-CH_2-$		1	H	H	NH_2
87		Direct bond		1	H	H	NH_2
88		$-CH_2-$		1	H	H	NH_2
89		$-(CH_2)_2-$		1	H	H	NH_2
90		$-CH_2-$		1	H	H	NH_2

Table 1 (10)



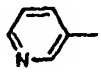
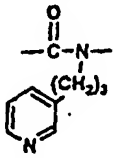
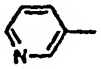
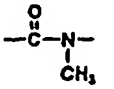
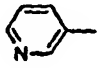
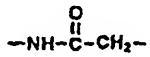
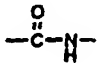
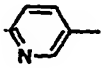
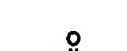
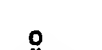
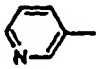
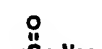
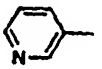
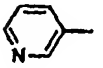
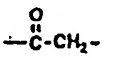
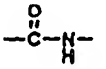
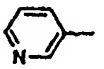
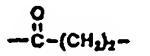
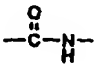
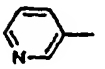
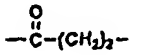
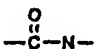
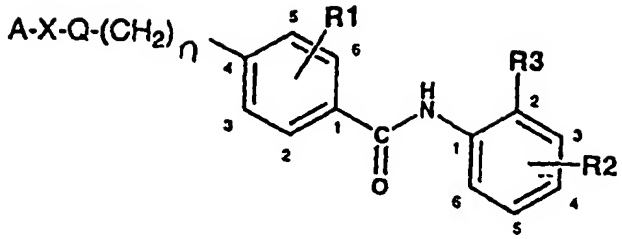
Compound No.	A	X	Q	n	R1	R2	R3
91		$-O-CH_2-$		1	H	H	NH_2
92		$-O-CH_2-$		1	H	H	NH_2
93				0	H	H	NH_2
94				1	H	H	NH_2
95				1	H	H	NH_2
96				0	H	H	NH_2
97				1	H	H	NH_2
98				0	H	H	NH_2
99				1	H	H	NH_2

Table 1 (11)



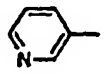
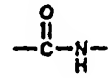
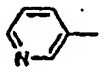
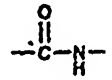
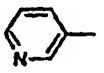
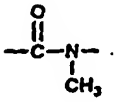
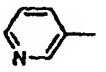
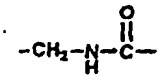
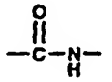
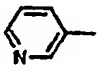
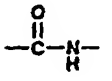
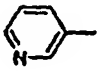
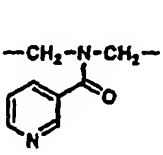
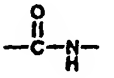
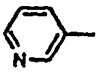
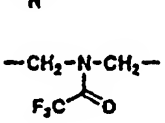
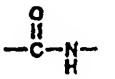
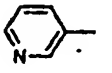
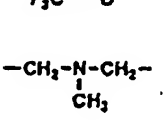
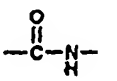
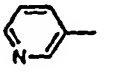
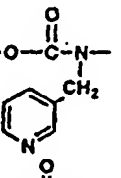
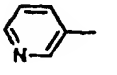
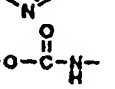
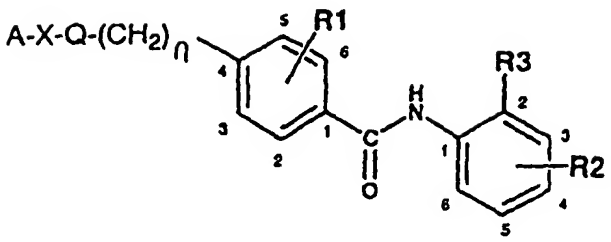
Compound No.	A	X	Q	n	R1	R2	R3
100		$-CH_2-O-CH_2-$		0	H	H	NH_2
101		$-CH_2-O-CH_2-$		0	3-CH_3	H	NH_2
102		$-CH_2-O-CH_2-$		0	H	H	NH_2
103				0	H	H	NH_2
104		$-CH_2-NH-CH_2-$		0	H	H	NH_2
105				0	H	H	NH_2
106				1	H	H	NH_2
107				0	H	H	NH_2
108		$-CH_2-$		1	H	H	NH_2
109		$-CH_2-$		1	H	5-F	NH_2

Table 1 (12)



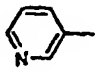
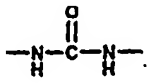
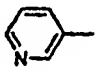
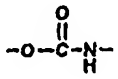
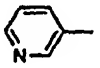
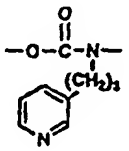
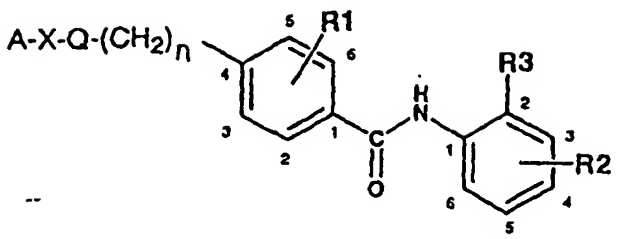
Compound No.	A	X	Q	n	R1	R2	R3
110		$-CH_2-$		1	H	5-F	NH_2
111		$-CH_2-$		1	H	4-Cl	NH_2
112		$-CH_2-$		1	H	H	NH_2

Table 1 (13)



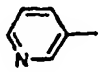
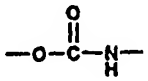
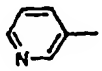
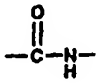
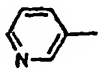
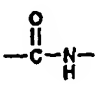
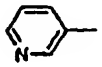
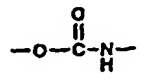
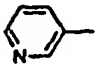
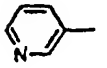
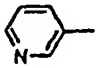
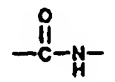
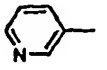
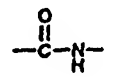
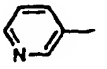
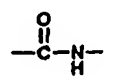
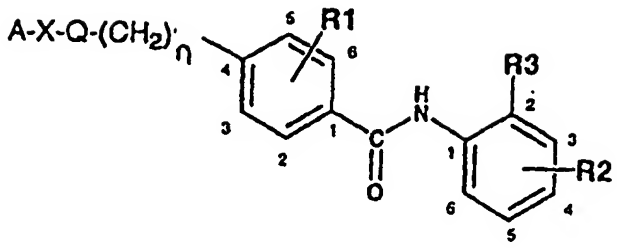
Compound No.	A	X	Q	n	R1	R2	R3
113		$-CH_2-$		1	H	5-OCH_3	NH_2
114		$-(CH_2)_3-$		0	H	5-F	NH_2
115		$-(CH_2)_2-$		0	3-Cl	H	NH_2
116		$-(CH_2)_2-$		0	H	H	NH_2
117				1	H	H	NH_2
118				1	H	H	NH_2
119		$-O-CH_2-$		1	2-Cl	H	NH_2
120		$-O-CH_2-$		1	H	5-F	NH_2
121		$-O-CH_2-$		1	H	5-OCH_3	NH_2

Table 1 (14)



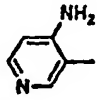
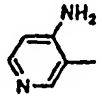
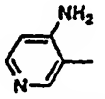
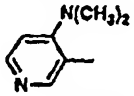
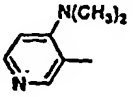
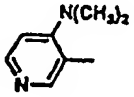
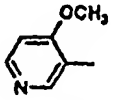
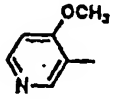
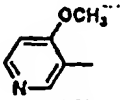
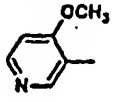
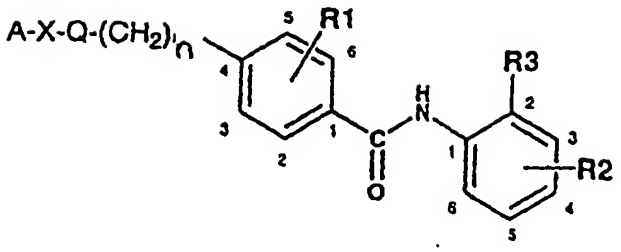
Compound No.	A	X	Q	n	R1	R2	R3
122		$-CH_2-$	$-O-\overset{O}{\overset{\|}{C}}-\underset{H}{N}-$	1	H	H	NH_2
123		$-O-CH_2-$	$-\overset{O}{\overset{\|}{C}}-\underset{H}{N}-$	1	H	H	NH_2
124		$-CH_2-O-CH_2-$	$-\overset{O}{\overset{\|}{C}}-\underset{H}{N}-$	1	H	H	NH_2
125		$-CH_2-$	$-O-\overset{O}{\overset{\|}{C}}-\underset{H}{N}-$	1	H	H	NH_2
126		$-O-CH_2-$	$-\overset{O}{\overset{\|}{C}}-\underset{H}{N}-$	1	H	H	NH_2
127		$-CH_2-O-CH_2-$	$-\overset{O}{\overset{\|}{C}}-\underset{H}{N}-$	1	H	H	NH_2
128		$-CH_2-$	$-O-\overset{O}{\overset{\|}{C}}-\underset{H}{N}-$	1	H	H	NH_2
129		$-O-CH_2-$	$-\overset{O}{\overset{\|}{C}}-\underset{H}{N}-$	1	H	H	NH_2
130		$-CH_2-O-CH_2-$	$-\overset{O}{\overset{\|}{C}}-\underset{H}{N}-$	1	H	H	NH_2
131		$-CH_2-$	$-O-\overset{O}{\overset{\|}{C}}-\underset{H}{N}-$	1	H	5-F	NH_2

Table 1 (15)



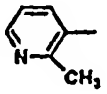
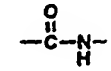
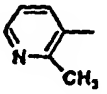
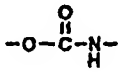
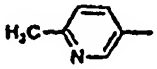
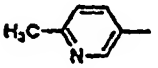
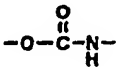
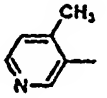
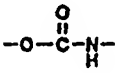
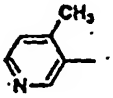
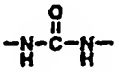
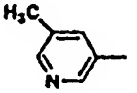
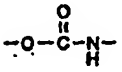
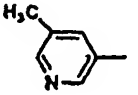
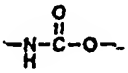
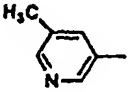
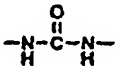
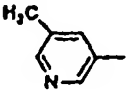
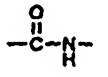
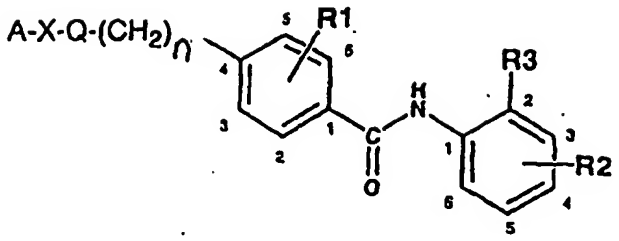
Compound No.	A	X	Q	n	R1	R2	R3
132		Direct bond		1	H	H	NH_2
133		$-CH_2-$		1	H	H	NH_2
134		Direct bond		1	H	H	NH_2
135		$-CH_2-$		1	H	H	NH_2
136		$-CH_2-$		1	H	H	NH_2
137		$-CH_2-$		1	H	H	NH_2
138		$-CH_2-$		1	H	H	NH_2
139		$-CH_2-$		1	H	H	NH_2
140		$-CH_2-$		1	H	H	NH_2
141		$-(CH_2)_2-$		1	H	H	NH_2

Table 1 (16)



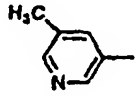
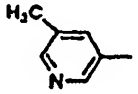
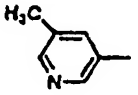
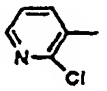
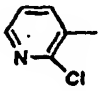
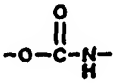
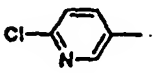
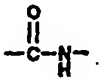
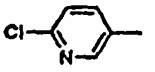
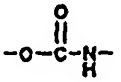
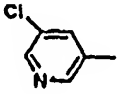
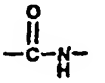
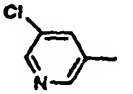
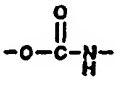
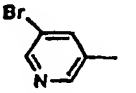
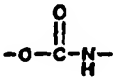
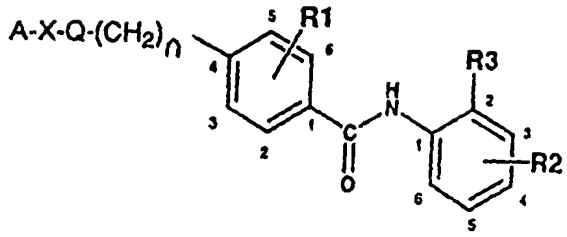
Compound No.	A	X	Q	n	R1	R2	R3
142		$-(CH_2)_2-$		1	H	H	NH_2
143		$-(CH_2)_2-$		0	H	H	NH_2
144		$-CH_2-$		2	H	H	NH_2
145		Direct bond		1	H	H	NH_2
146		$-CH_2-$		1	H	H	NH_2
147		Direct bond		1	H	H	NH_2
148		$-CH_2-$		1	H	H	NH_2
149		$-O-CH_2-$		1	H	H	NH_2
150		$-O-CH_2-$		1	H	H	NH_2
151		$-CH_2-$		1	H	H	NH_2

Table 1 (17)



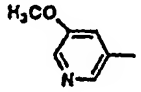
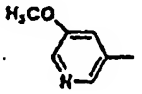
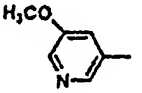
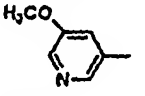
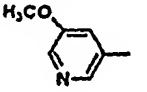
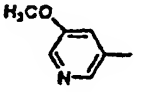
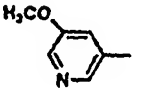
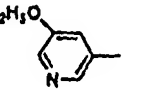
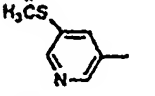
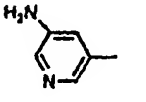
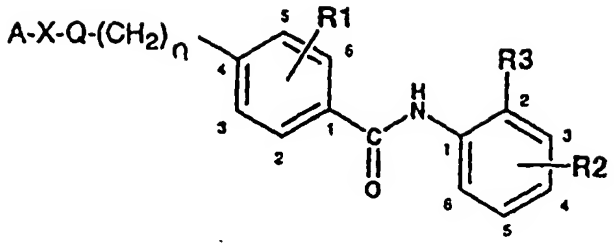
Compound No.	A	X	Q	n	R1	R2	R3
152		$-CH_2-$	$-O-\overset{O}{\overset{\|}{C}}-\overset{H}{N}-$	1	H	H	NH_2
153		$-CH_2-$	$-\overset{H}{N}-\overset{O}{\overset{\|}{C}}-O-$	1	H	H	NH_2
154		$-CH_2-$	$-\overset{H}{N}-\overset{O}{\overset{\|}{C}}-\overset{H}{N}-$	1	H	H	NH_2
155		$-(CH_2)_2-$	$-\overset{O}{\overset{\|}{C}}-\overset{H}{N}-$	1	H	H	NH_2
156		$-(CH_2)_2-$	$-\overset{O}{\overset{\|}{C}}-\overset{H}{N}-$	1	H	H	NH_2
157		$-(CH_2)_2-$	$-\overset{H}{N}-\overset{O}{\overset{\|}{C}}-$	0	H	H	NH_2
158		$-CH_2-$	$-\overset{H}{N}-\overset{O}{\overset{\|}{C}}-$	2	H	H	NH_2
159		$-CH_2-$	$-O-\overset{O}{\overset{\|}{C}}-\overset{H}{N}-$	1	H	H	NH_2
160		$-CH_2-$	$-O-\overset{O}{\overset{\|}{C}}-\overset{H}{N}-$	1	H	H	NH_2
161		$-CH_2-$	$-O-\overset{O}{\overset{\|}{C}}-\overset{H}{N}-$	1	H	H	NH_2

Table 1 (18)



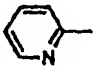
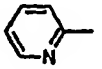
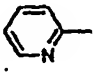
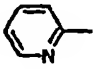
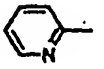
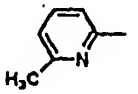
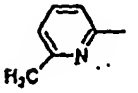
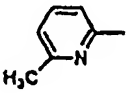
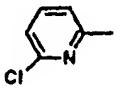
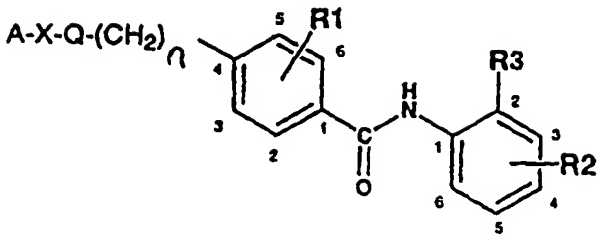
Compound No.	A	X	Q	n	R1	R2	R3
162		$-CH_2-$	$-O-\overset{O}{\overset{\|\|}{C}}-\underset{H}{N}-$	1	H	H	NH_2
163		$-(CH_2)_2-$	$-O-\overset{O}{\overset{\|\|}{C}}-\underset{H}{N}-$	1	H	H	NH_2
164		Direct bond	$-\overset{O}{\overset{\|\|}{C}}-\underset{H}{N}-$	1	H	H	NH_2
165		$-CH_2-$	$-\overset{O}{\overset{\|\|}{C}}-\underset{H}{N}-$	0	H	H	NH_2
166		$-O-CH_2-$	$-\overset{O}{\overset{\|\|}{C}}-\underset{H}{N}-$	1	H	5-OCH_3	NH_2
167		$-CH_2-O-CH_2-$	$-\overset{O}{\overset{\|\|}{C}}-\underset{H}{N}-$	0	H	H	NH_2
168		$-CH_2-$	$-\overset{O}{\overset{\|\|}{C}}-\underset{H}{N}-$	0	H	H	NH_2
169		Direct bond	$-\overset{O}{\overset{\|\|}{C}}-\underset{H}{N}-$	1	H	H	NH_2
170		$-CH_2-$	$-O-\overset{O}{\overset{\|\|}{C}}-\underset{H}{N}-$	1	H	H	NH_2
171		$-CH_2-$	$-O-\overset{O}{\overset{\|\|}{C}}-\underset{H}{N}-$	1	H	H	NH_2

Table 1 (19)



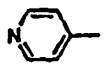
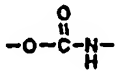
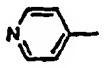
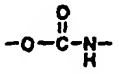
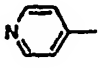
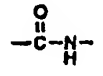
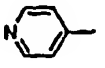
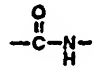
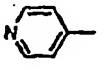
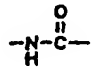
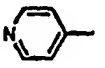
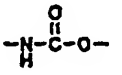
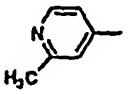
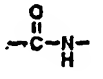
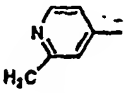
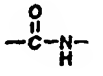
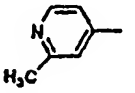
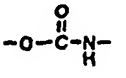
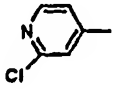
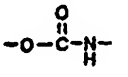
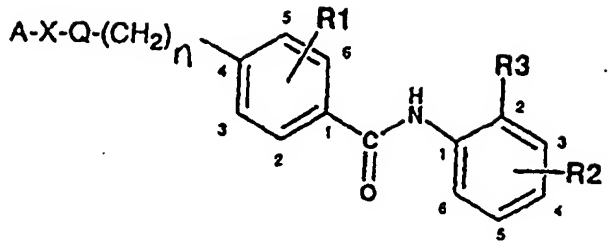
Compound No.	A	X	Q	n	R1	R2	R3
172		$-CH_2-$		1	H	H	NH_2
173		$-(CH_2)_2-$		1	H	H	NH_2
174		Direct bond		1	H	H	NH_2
175		$-CH_2-$		0	H	H	NH_2
176		$-CH_2-$		0	H	H	NH_2
177		$-CH_2-$		1	H	H	NH_2
178		$-CH_2-$		0	H	H	NH_2
179		Direct bond		1	H	H	NH_2
180		$-CH_2-$		1	H	H	NH_2
181		$-CH_2-$		1	H	H	NH_2

Table 1 (20)



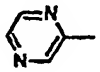
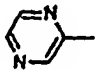
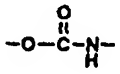
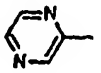
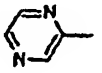
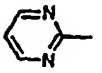
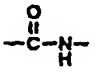
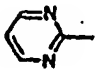
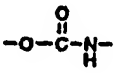
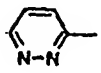
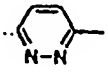
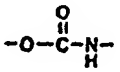
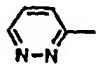
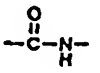
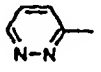
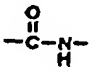
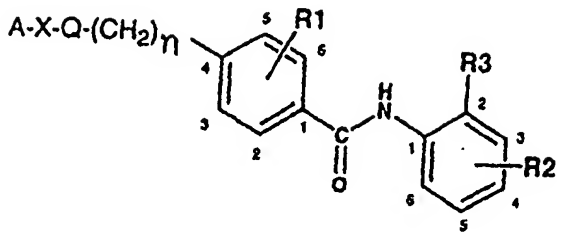
Compound No.	A	X	Q	n	R1	R2	R3
182		Direct bond		1	H	H	NH_2
183		$-CH_2-$		1	H	H	NH_2
184		$-CH_2-O-CH_2-$		1	H	H	NH_2
185		$-CH_2-O-CH_2-$		0	H	H	NH_2
186		Direct bond		1	H	H	NH_2
187		$-CH_2-$		1	H	H	NH_2
188		Direct bond		1	H	H	NH_2
189		$-CH_2-$		1	H	H	NH_2
190		$-CH_2-O-CH_2-$		1	H	H	NH_2
191		$-CH_2-O-CH_2-$		0	H	H	NH_2

Table 1 (21)



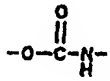
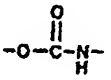
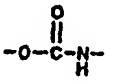
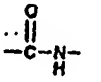
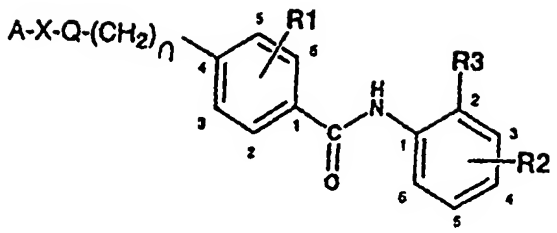
Compound No.	A	X	Q	n	R1	R2	R3
192		Direct bond		1	H	H	NH_2
193		$-CH_2-$		1	H	H	NH_2
194		$-(CH_2)_2-$		1	H	H	NH_2
195		$-CH_2-O-CH_2-$		0	H	H	NH_2
196		Direct bond		1	H	H	NH_2
197		$-CH_2-$		1	H	H	NH_2
198		$-CH_2-O-CH_2-$		1	H	H	NH_2
199		$-CH_2-O-CH_2-$		0	H	H	NH_2
200		Direct bond		1	H	H	NH_2
201		Direct bond		1	H	H	NH_2

Table 1 (22)



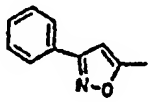
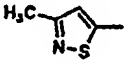
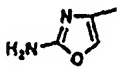
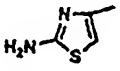
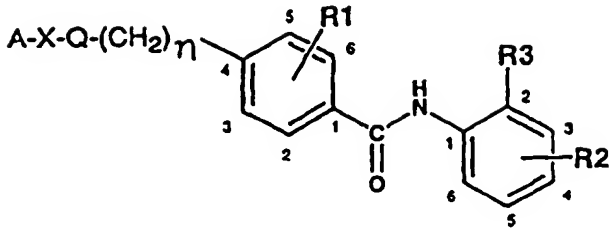
Compound No.	A	X	Q	n	R1	R2	R3
202		$-CH_2-$	$-O-\overset{O}{\overset{\|}{C}}-\underset{H}{N}-$	1	H	H	NH_2
203		Direct bond	$-\overset{O}{\overset{\|}{C}}-\underset{H}{N}-$	1	H	H	NH_2
204		Direct bond	$-\overset{O}{\overset{\|}{C}}-\underset{H}{N}-$	1	H	H	NH_2
205		Direct bond	$-\overset{O}{\overset{\|}{C}}-\underset{H}{N}-$	1	H	H	NH_2
206		$-(CH_2)_2-$	$-\underset{H}{N}-\overset{O}{\overset{\|}{C}}-O-$	1	H	H	NH_2
207		$-CH_2-$	$-O-\overset{O}{\overset{\|}{C}}-\underset{H}{N}-$	1	H	H	NH_2
208		$-(CH_2)_2-$	$-O-\overset{O}{\overset{\|}{C}}-\underset{H}{N}-$	1	H	H	NH_2
209		$-CH_2-$	$-O-\overset{O}{\overset{\|}{C}}-\underset{H}{N}-$	1	H	H	NH_2
210		$-CH_2-$	$-O-\overset{O}{\overset{\|}{C}}-\underset{H}{N}-$	1	H	H	NH_2
211		$-CH_2-$	$-\overset{O}{\overset{\|}{C}}-\underset{H}{N}-$	1	H	H	NH_2

Table 1 (23)



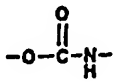
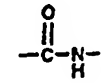
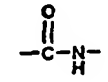
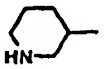
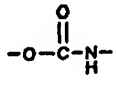
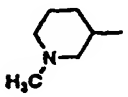
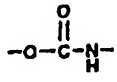
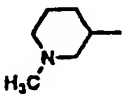
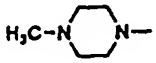
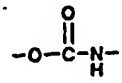
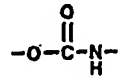
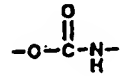
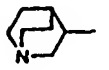
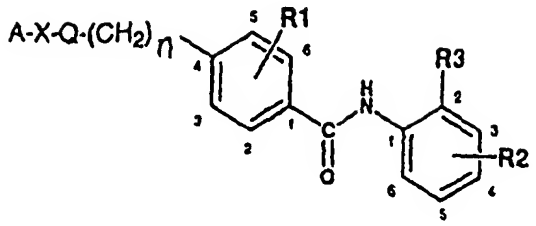
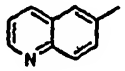
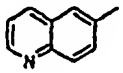
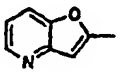
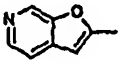
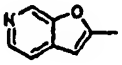
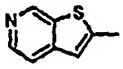
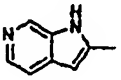
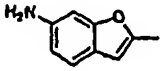
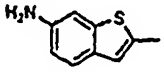
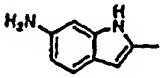
Compound No.	A	X	Q	n	R1	R2	R3
212		$-CH_2-$		1	H	H	NH_2
213		$-CH_2-O-CH_2-$		1	H	H	NH_2
214		$-CH_2-O-CH_2-$		1	H	H	NH_2
215		Direct bond		1	H	H	NH_2
216		$-CH_2-$		1	H	H	NH_2
217		$-CH_2-O-CH_2-$		1	H	H	NH_2
218		$-(CH_2)_3-$		1	H	H	NH_2
219		Direct bond		1	H	H	NH_2
220		$-CH_2-$		1	H	H	NH_2
221		$-CH_2-O-CH_2-$		1	H	H	NH_2

Table 1 (24)



Compound No.	A	X	Q	n	R1	R2	R3
222		Direct bond		1	H	H	NH_2
223		Direct bond		1	H	H	NH_2
224		Direct bond		1	H	H	NH_2
225		Direct bond		1	H	H	NH_2
226		Direct bond		1	H	H	NH_2
227		Direct bond		1	H	H	NH_2
228		Direct bond		1	H	H	NH_2
229		Direct bond		1	H	H	NH_2
230		Direct bond		1	H	H	NH_2
231		Direct bond		1	H	H	NH_2

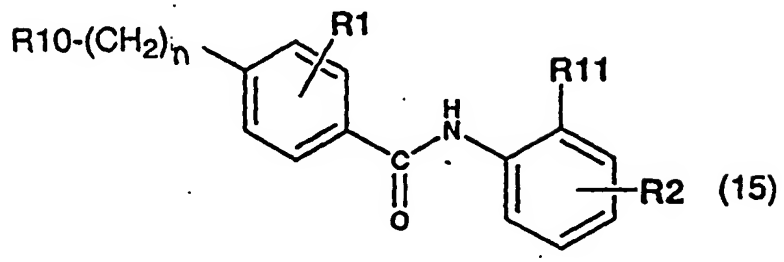
[0037] The compound of this invention may be prepared as described below.

(a) A compound represented by formula (14);

$$A\text{-}X\text{-}R^9 \qquad (14)$$

wherein A and X are as defined above; R^9 is -C(=G)OH (G is an oxygen or sulfur atom) or $-NH_2$;

is condensed with a compound represented by formula (15);



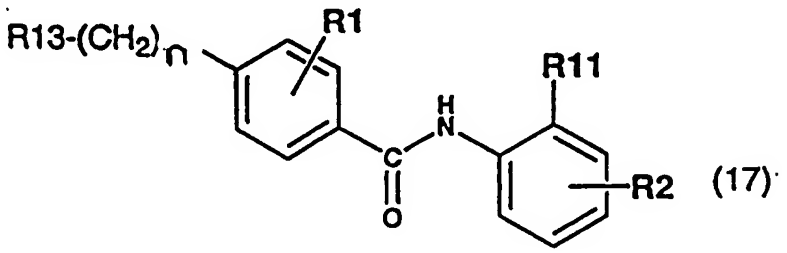
(15)

wherein R^1, R^2 and n are as defined above; R^{10} is $-NH_2$ when R^9 is -C(=G)OH (G is as defined above) and -C(=G)OH (G is as defined above) when R^9 is $-NH_2$; R^{11} is an amino group protected with a protective group used in a common peptide-forming reaction, e.g., tert-butoxycarbonyl or a hydroxyl group protected with a protecting group commonly used in a peptide-forming reaction, including benzyl.

(b) A compound represented by formula (16)

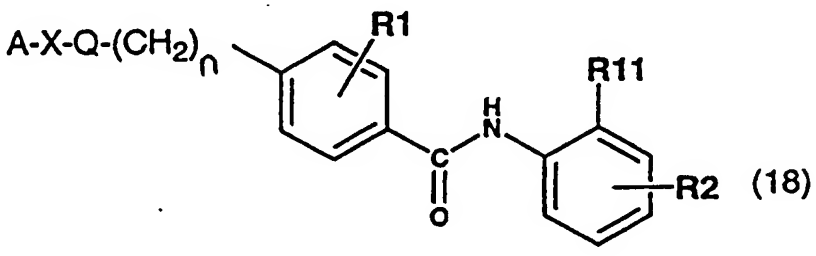
$$A\text{-}X\text{-}R^{12} \qquad (16)$$

wherein A and X are as defined above; and R^{12} is -OH or $-NH_2$;
is condensed with a compound represented by formula (17);



(17)

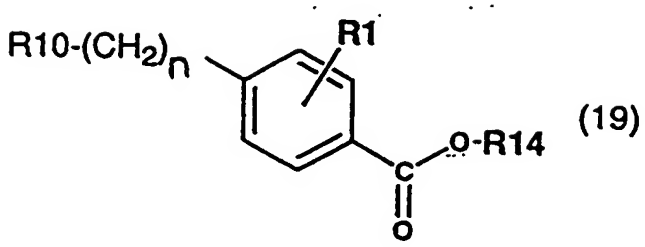
wherein R^1, R^2, R^{11} and n are as defined above; R^{13} is -OH or $-NH_2$;
using an agent such as N,N'-carbonyldiimidazole, N,N'-thiocarbonyldiimidazole, phosgene or thiophosgene, to give a compound represented by formula (18);



(18)

wherein A, X, Q, n, R^1, R^2 and R^{11} are as defined above, whose protecting group is then removed to give the compound of this invention.

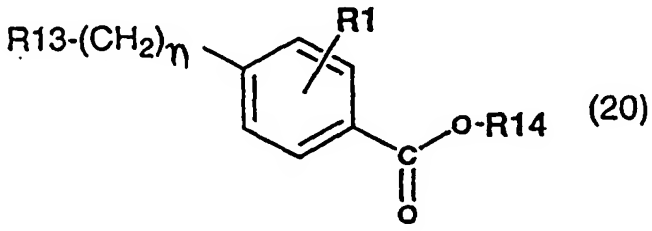
(c) A compound represented by formula (14) is condensed with a compound represented by formula (19);



(19)

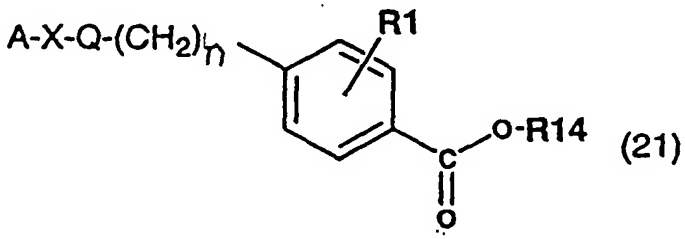
wherein R^1, R^{10} and n are as defined above; R^{14} is a methyl, ethyl or tert-butyl group.

(d) A compound represented by formula (16) is condensed with a compound represented by formula (20);



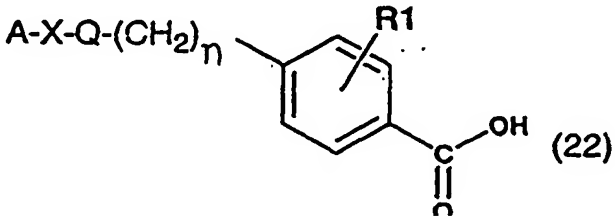
(20)

wherein R^1, R^{13}, R^{14} and n are as defined above; using an agent such as N,N'-carbonyldiimidazole, N,N'-thiocarbonyldiimidazole, phosgene or thiophosgene to give a compound represented by formula (21);



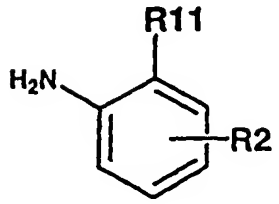
(21)

wherein A, X, Q, n, R^1 and R^{14} are as defined above; which is then hydrolyzed to give a compound represented by formula (22);



(22)

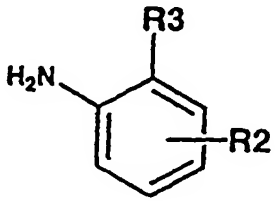
wherein A, X, Q, n and R^1 are as defined above. The product is condensed with a compound represented by formula (23);



(23)

wherein R^2 and R^{11} are as defined above; to give a compound represented by formula (18) whose protecting group is then removed to give the compound of this invention.

(e) A compound represented with formula (22) is condensed with a compound represented by formula (24);

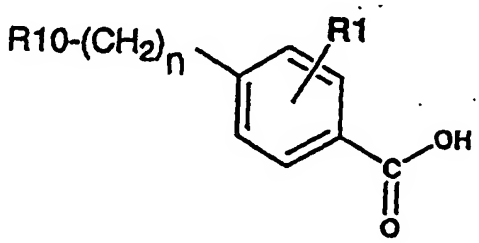


(24)

wherein R^2 and R^3 are as defined above; to give the compound of this invention.

[0038] Preparation procedures for typical intermediates are shown below.

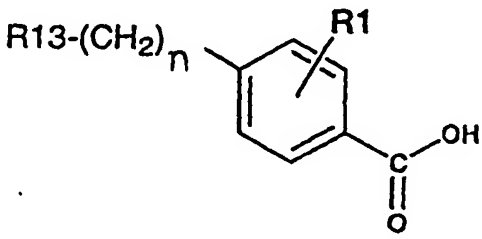
[0039] A compound represented by formula (15) may be prepared by introducing an appropriate protecting group to a benzoic acid derivative represented by formula (25);



(25)

wherein R^1, R^{10} and n are as defined above; condensing the product with a compound represented by formula (23), and removing the protecting group of the condensation product.

[0040] A compound represented by formula (17) may be prepared by introducing an appropriate protecting group to a benzoic acid derivative represented by formula (26) ;



(26)

wherein R^1, R^{13} and n are as defined above; condensing the product with a compound represented by formula (23), and removing the protecting group of the condensation product.

[0041] A compound represented by formula (23) may be prepared by introducing a protecting group to a compound represented by formula (24).

[0042] Next, reactions used for preparation of the compound of this invention will be described.

[0043] The condensation reaction in (a) may be an amide-bond forming reaction for a usual peptide using, for example, an activated ester, a mixed acid anhydride or an acid halide. For example, a carboxylic acid, i.e., a compound represented by formula (14) wherein R^9 is -C(=G)OH (G is as defined above) or a compound represented by formula (15) wherein R^{10} is -C(=G)OH (G is as defined above), may be condensed with a phenol derivative such as 2,4,5-trichlorophenol, pentachlorophenol and 4-nitrophenol, or an N-hydroxy compound such as N-hydoxysuccinimide and N-hydroxybenzotriazole, in the presence of dicyclohexylcarbodiimide, to be converted into an activated ester, which is then condensed with an amine represented by formula (14) wherein R^9 is $-NH_2$ or by formula (15) wherein R^{10} is $-NH_2$, to give the desired product.

[0044] Alternatively, a carboxylic acid represented by formula (14) wherein R^9 is -C(=G)OH (G is as defined above) or by formula (15) wherein R^{10} is -C(=G)OH (G is as defined above), may be reacted with, for example, oxalyl chloride, thionyl chloride or phosphorus oxychloride to be converted into an acid chloride, which is then condensed with an amine represented by formula (14) wherein R^9 is $-NH_2$ or by formula (15) wherein R^{10} is $-NH_2$, to give the desired product.

[0045] Furthermore, a carboxylic acid represented by formula (14) wherein R^9 is -C(=G)OH (G is as defined above) or by formula (15) wherein R^{10} is -C(=G)OH (G is as defined above), may be reacted with, for example, isobutyl chlorocarbonate or methanesulfonyl chloride to be converted into a mixed acid anhydride, which is then condensed with an amine represented by formula (14) wherein R^9 is $-NH_2$ or by formula (15) wherein R^{10} is $-NH_2$, to give the desired product.

[0046] The above condensation reaction may be conducted solely using a peptide condensing agent such as dicyclohexylcarbodiimide, N,N'-carbonyldiimidazole, diphenyl phosphoric azide, diethylphosphorylcyanide, 2-chloro-1,3-dimethylimidazolonium chloride, etc.

[0047] The reaction may be usually conducted at -20 to +50 °C for 0.5 to 48 hours. Solvents which may be used include aromatic hydrocarbons such as benzene, toluene and the like; ethers such as tetrahydrofuran, dioxane, diethyl ether and the like; halogenated hydrocarbons such as dichloromethane, chloroform and the like; N,N-dimethylformamide; alcohols such as methanol, ethanol and the like; and a mixture thereof. If necessary, an organic base such as triethylamine and pyridine may be added.

[0048] The condensation reaction in (b) may be conducted by activating a compound represented by either formula (16) or (17) with, for example, phosgene, thiophosgene, N,N'-carbonyldiimidazole, N,N'-thiocarbonyldiimidazole or the like and then reacting the activated product with the other compound. The reaction may be usually conducted at -20 to +50 °C for 0.5 to 48 hours. Solvents which may be used include aromatic hydrocarbons such as benzene, toluene and the like; ethers such as tetrahydrofuran, dioxane, diethyl ether and the like; halogenated hydrocarbons such as dichloromethane, chloroform and the like; N,N-dimethylformamide; and a mixture thereof. If necessary, an organic base such as triethylamine, pyridine and the like may be added.

[0049] The condensation reaction in (c) may be conducted as the condensation in (a).

[0050] The condensation reaction in (d) may be conducted as the condensation in (b).

[0051] The protecting group of the compound represented by formula (17) may be removed under the conditions used in a common peptide-forming reaction. For example, when R^{11} in formula (18) is the amino group protected with tert-butoxycarbonyl, it may be deprotected by treatment with an acid such as hydrochloric acid, trifluoroacetic acid or the like.

[0052] A salt of a compound represented by formula (1) may be formed during preparation of the compound, but is usually formed by treating the compound with a pharmaceutically acceptable acid. Such an acid includes inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid and the like; and organic acids such as acetic acid, tartaric acid, fumaric acid, maleic acid, citric acid, benzoic acid, trifluroacetic acid, p-toluenesulfonic acid and the like. These salts may be also used as an active ingredient in this invention, as the free base, the compound represented by formula (1).

[0053] A compound represented by formula (1) may be purified or isolated by a usual separation method such as extraction, recrystallization, column chromatography and the like.

[0054] The novel benzamide derivative of this invention has differentiation-inducing effect and thus is useful as a therapeutic and/or improving agent to a variety of diseases such as malignant tumors, autoimmune diseases, dermatologic diseases and parasitism.

[0055] As used herein, a "malignant tumor" includes hematologic malignancy such as acute leukemia, malignant lymphoma, multiple myeloma and macroglobulinemia as well as solid tumors such as colon cancer, cerebral tumor, head and neck tumor, breast carcinoma, pulmonary cancer, esophageal cancer, gastric cancer, hepatic cancer, gallbladder cancer, bile duct cancer, pancreatic cancer, nesidioblastoma, renal cell carcinoma, adrenocortical cancer, urinary bladder carcinoma, prostatic cancer, testicular tumor, ovarian carcinoma, uterine cancer, chorionic carcinoma, thyroid cancer, malignant carcinoid tumor, skin cancer, malignant melanoma, osteogenic sarcoma, soft tissue sarcoma, neuroblastoma, Wilms tumor and retinoblastoma.

[0056] An autoimmune disease includes rheumatism, diabetes, systemic lupus erythematodes, human autoimmune lymphocytotic lymphadenopathy, immunoblastic lymphadenopathy, Crohn disease and ulcerative colitis.

[0057] A dermatologic disease includes psoriasis, acne, eczema and atopic dermatitis.

[0058] Parasitism includes diseases such as malaria caused through vermination.

[0059] Indications for the compound of this invention are not limited to these specific examples.

[0060] The active ingredient of this invention useful as a drug may be used in the form of a general pharmaceutical composition. The pharmaceutical composition may be prepared with generally used diluents or excipients such as filler, extender, binder, moisturizing agent, disintegrator, surfactant and lubricant. The pharmaceutical composition may have a variety of dosage forms depending on its therapeutic purpose; typically tablet, pill, powder, solution, suspension, emulsion, granule, capsule, injection (e.g., solution, suspension) and suppository.

[0061] For preparing tablets, a variety of carriers well-known in the art may be used. Such a carrier includes excipients such as lactose, glucose, starch, calcium carbonate, kaoline, crystalline cellulose and silicic acid; binders such as water, ethanol, propanol, simple syrup, glucose solution, starch solution, gelatin solution, carboxymethyl cellulose, shellac, methyl cellulose and polyvinyl pyrrolidone; disintegrators such as dried starch, sodium alginate, powdered agar, calcium carmelose, starch and lactose; disintegration retarders such as sucrose, cocoa butter and hydrogenated oil; absorption promoters such as quaternary ammonium base and sodium lauryl sulfate; moisturizing agents such as glycerin and starch; adsorbents such as starch, lactose, kaoline, bentonite, colloidal silicic acid; and glidants such as talc, stearates and polyethylene glycol. The tablet may be, if necessary, one coated with a common coating; for example, sugar-coated tablet, gelatin-coated tablet, enteric coated tablet, film-coated tablet, double-layer tablet and multilayer tablet.

[0062] In forming pills, a variety of carriers well-known in the art may be used. Such a carrier includes excipients such as crystalline cellulose, lactose, starch, hydrogenated vegetable oil, kaoline and talc; binders such as powdered acacia, powdered tragacanth gum and gelatin; disintegrators such as calcium carmelose and agar.

[0063] Capsule may be prepared by blending an active ingredient with a variety of the above carriers as usual and filling the resulting blend into, for example, a hard or soft gelatin capsule or the like.

[0064] For preparing injection, solution, emulsion and suspension are sterilized and preferably isotonic with blood. It may be prepared using diluents commonly used in the art; for example, water, ethanol, macrogol, propylene glycol, ethoxylated isostearyl alcohol, polyoxyisostearyl alcohol and polyoxyethylene sorbitan fatty acid esters. The pharmaceutical preparation may contain sodium chloride necessary to prepare an isotonic solution, glucose or glycerin, as well as usual solubilizers, buffers and soothing agents.

[0065] Suppository may be formed using a variety of well-known carriers; for example, semi-synthetic glyceride, cocoa butter, higher alcohols, higher alcohol esters and polyethylene glycol.

[0066] Furthermore, the pharmaceutical composition may contain coloring agents, preservatives, perfumes, flavors, sweeteners and/or other drugs.

[0067] The amount of the active ingredient in the pharmaceutical composition of this invention may be, as appropriate, selected from a wide range with no limitations, and is generally about 1 to 70 % by weight in the composition, preferably about 5 to 50 % by weight.

[0068] An administration route of the pharmaceutical composition is not limited, and selected depending on patient's age, sex, severity of disease and other conditions. For example, tablet, pill, solution, suspension, emulsion, granule and capsule may be orally administered; injection may be intravenously administered solely or in combination with a common infusion fluid such as glucose, amino acids and the like, or if necessary, intramuscularly, subcutaneously or intraperitoneally as a sole preparation. Suppository may be intrarectally administered.

[0069] Dose of the pharmaceutical preparation of this invention may be selected, depending on their dosage form, patient's age, sex and severity of disease, and other conditions, as appropriate, but the amount of the active ingredient may be generally about 0.0001 to 100 mg/kg a day. It is recommended that a unit dosage form may contain about 0.001 to 1000 mg of the active ingredient.

[0070] The compound represented by formula (1) of this invention or a salt thereof exhibits no or a mall toxicity which is acceptable as the anticancer agent at the dose showing pharmacological effects.

Examples

[0071] This invention will be specifically illustrated with, but is not limited to, the following examples, where the numbers in parentheses indicate those of the compounds shown in the above detailed description.

Example 1

Preparation of N-(2-aminophenyl)-4-(N-benzoylaminomethyl)benzamide hydrochloride (Table 1: hydrochloride of Compound 1):

[0072]

(1-1) To a suspension of 21.16 g of 4-aminomethylbenzoic acid(140 mmol) in 450 mL of dichloromethane was added 42 mL of triethylamine (300 mmol). Under ice-cooling, 60.4 g of trifluoroacetic anhydride (287 mmol) in 50 mL of dichloromethane were added dropwise, maintaining the inner temperature at 3 to 8 °C, and then the mixture was stirred four 3 hours. The reaction mixture was poured into a saturated aqueous sodium bicarbonate solution, and was acidified with 10 % hydrochloric acid. The gel precipitate was collected by filtration and dried to give 30.4g of 4-(N-trifluoroacetylaminomethyl)benzoic acid (Yield: 87.8 %) as an opalescent solid.

^{1}H NMR (270MHz, DMSO-d_6) δ ppm: 4.47(2H, d, J=5.8 Hz), 7.39(2H, d, J=8.1 Hz), 7.93(2H, d, J=8.1 Hz), 10.08(1H, t, J=5.8 Hz), 12.95(1H, br.s.)

(1-2) To a solution of 108 g of o-phenylenediamine (1.0 mol) in 1000 mL of dioxane was added 500 mL of 1N sodium hydroxide aq., and then 218 g of tert-butyldicarbonate (1.1 mol) in 500 mL of dioxane under ice-cooling. After stirring for 6 hours at room temperature, the mixture was left overnight. The mixture was concentrated to 1/2 volume by evaporation, and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried and evaporated. The residue was purified by column chromatography (eluent: chloroform) to give a solid, which was then washed with diethyl ether to give 68.4 g of N-tert-butoxycarbonyl-o-phenylenediamine (Yield: 32.8 %) as a white solid.

^{1}H NMR (270 MHz, $CDCl_3$) δ ppm: 1.51(9H, s), 3.75(2H, s), 6.26(1H, s), 6.77(1H, d, J=8.1 Hz), 6.79(1H, dd, J=7.3, 8.1 Hz), 7.00(1H, dd, J=7.3, 8.1 Hz), 7.27(1H, d, J=8.1 Hz)

(1-3) To a suspension of 30 g of the compound from the process (1-1) (121 mmol) in 200 mL of dichloromethane were slowly added dropwise 21 g of oxalyl chloride (165 mmol) with intermittently adding DMF (0.1 mL per 2 mL addition), maintaining the inner temperature within 10 to 15 °C by ice-cooling. After completion of the addition, the mixture was stirred until bubble generation ceased, and then at 40 °C for an additional hour. After evaporation, excess oxalyl chloride was azeotropically removed with toluene, and then the residue was redissolved in 100 mL of dichloroethane. The prepared acid chloride solution was added dropwise to a solution of 22.88 g of the compound from the process (1-2) (110 mmol) in 100 mL of dichloromethane and 200 mL of pyridine, maintaining the inner temperature within 7 to 9 °C by ice-cooling.

After addition, the mixture was warmed to room temperature, and was left overnight. After adding saturated sodium bicarbonate aq. to the reaction mixture, the resulting mixture was extracted with chloroform, and the organic layer was washed with saturated brine, dried and evaporated. To the residue was added methanol-diisopropyl ether, and the precipitated solid was collected by filtration and dried to give 28.1 g of N-[2-(N-tert-butoxycarbonyl) aminophenyl]-4-(N-trifluoroacetylaminomethyl)benzamide (Yield: 58 %) as a light yellow solid.

^{1}H NMR (270 MHz, DMSO-d_6) δ ppm: 1.44(9H, s), 4.48(2H, d, J=5.9 Hz), 7.12-7.23(2H, m), 7.44(2H, d, J=8.1 Hz), 7.54(2H, d, J=8.1 Hz), 7.94(2H, d, J=8.1 Hz), 8.68(1H, br.s), 9.83(1H, s), 10.10(1H, br.t, J=5.9 Hz)

(1-4) To a suspension of 13.12 g of the compound from the process (1-3) (30 mmol) in 120 mL of methanol and 180 mL of water were added 4.70 g of potassium carbonate (34.0 mmol), and the mixture was heated with stirring at 70 °C for 4 hours. It was extracted with chloroform, and the organic layer was washed with saturated brine, dried, evaporated and dried to give 10.3 g of 4-aminomethyl-N-[2-(N-tert-butoxycarbonyl)aminophenyl]benzamide (Yield: quantitative) as a light yellow amorphous solid.

^{1}H NMR (270 MHz, DMSO-d_6) δ ppm: 3.80(2H, s), 7.13-7.23(2H, m), 7.48-7.58(4H, m), 7.90(2H, d, J=8.1 Hz), 8.69(1H, br.s), 9.77(1H, br.s)

(1-5) To a solution of 0.11 g of the compound from the process (1-4) (0.44 mmol) in 5 mL of pyridine was added 0.08 g of benzoyl chloride (0.53 mmol), and the mixture was gradually warmed to room temperature and then stirred for 8 hours. Saturated sodium bicarbonate aq. was added, and then the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried and evaporated. The residue was washed with diisopropyl ether, and the solid obtained was dried to give 0.14 g of N-[2-(N-tert-butoxycarbonyl)aminophenyl]-4-(N-benzoylaminomethyl)benzamide (Yield: 71.4 %) as a white solid.

^{1}H NMR (270 MHz, DMSO-d_6) δ ppm: 1.44(9H, s), 4.56(2H, d, J=5.9 Hz), 7.11-7.22(2H, m), 7.46-7.56(7H, m), 7.90-7.94(4H, m), 8.67(1H, s), 9.15(1H, t, J=5.9 Hz), 9.81(1H, s)

(1-6) To a solution of 0.10 g of the compound from the process (1-5) (0.224 mmol) in 5 mL of dioxane and 1 mL of methanol was added 5 mL of 4N hydrochloric acid-dioxane, and the mixture was stirred at room temperature for 7 hours. To the residue after evaporation was added diisopropyl ether, and the formed solid was collected by filtration and dried to give 0.08 g of N-(2-aminophenyl)-4-(N-benzoylaminomethyl)benzamide hydrochloride (Yield:

93 %) as a light brown solid.
mp: 206-209 °C
^{1}H NMR (270 MHz, DMSO-d_6) δ ppm: 4.57(2H, d, J=5.8 Hz), 7.27-7.38(4H, m), 7.47-7.59(5H, m), 7.92(1H, d, J=8.1 Hz), 8.05(1H, d, J=8.1 Hz), 9.19(1H, t, J=5.8 Hz), 10.38(1H, br.s)
IR(KBr, cm^{-1}): 3286, 3003(br.), 1630, 1551, 1492, 1306, 1250, 749, 695.

[0073] As described in Example 1, the compounds of Examples 2 to 41 were prepared, each of whose melting point (mp), ^{1}H NMR data and/or IR data are described below.

Example 2

N-(2-aminophenyl)-4-[N-(2-chlorobenzoyl)aminomethyl]benzamide (Table 1: Compound 14)

[0074]

mp: 201-204 °C(dec.).
^{1}H NMR (270MHz, DMSO-d_6) δ ppm: 4.52(2H, t, J=5.9 Hz), 4.89(2H, br.s), 6.60(1H, ddd, J=1.5, 7.3, 8.1 Hz), 6.78 (1H, dd, J=1.5, 8.1 Hz), 6.97(1H, ddd, J=1.5, 7.3, 8.1Hz), 7.17(1H, d, J=8.1Hz), 7.38-7.54(6H, m), 7.97(2H, d, J=8.1 Hz), 9.06(1H, br.t, J=5.9 Hz), 9.63(1H, br.s)
IR (KBr) cm^{-1}: 3268, 1649, 1458, 1304, 748

Example 3

N-(2-aminophenyl)-4-[N-(2-nitrobenzoyl)aminomethyl]benzamide hydrochloride(Table 1: hydrochloride of Compound 18)

[0075]

mp: 210-212 °C(dec.)
^{1}H NMR(270MHz, DMSO-d_6) δ ppm : 4.55(2H, t, J=5.9Hz), 7.20-7.40(3H, m), 7.50-7.60(1H, m), 7.53(2H, d, J=8.1 Hz), 7.60-7.70(2H, m), 7.83(1H, ddd, J=1.5, 8.1, 8.1Hz), 8.00-8.10(3H, m), 9.34(1H, t, J=5.9 Hz), 10.43(1H, br.s)
IR(KBr)cm^{-1}: 3283, 2500-3000(br.), 1648, 1534, 1461, 1362, 1314, 754, 701

Example 4

N-(2-aminophenyl)-4-[N-(4-methylbenzoyl)aminomethyl]benzamide hydrochloride (Table 1: hydrochloride of Compound 28)

[0076]

mp:(amorphous).
^{1}H NMR(270MHz, DMSO-d_6) δ ppm : 2.37(3H, s), 4.56(2H, d, J=5.0 Hz), 7.2.0-7.30(6H, m), 7.47(4H, d, J=8.8 Hz), 7.82(2H, d, J=8.8 Hz), 8.03(2H, d, J=8.8 Hz), 9.09(1H, t, J=5 Hz), 10.36(1H, br.s)
IR(KBr)cm^{-1}: 3269(br.), 2861(br.), 1743, 1636, 1534, 1505, 1456, 1308, 1120, 753.

Example 5

N-(2-aminophenyl)-4-[N-(3-methoxybenzoyl)aminomethyl]benzamide (Table 1: Compound 30)

[0077]

mp: 182-185 °C
^{1}H NMR(270MHz, DMSO-d_6) δ ppm: 3.81(3H, s), 4.54(2H, d, J=5.9 Hz), 4.88(2H, br.s), 6.60(1H, dd, J=6.6, 7.3 Hz), 6.78(1H, d, J=7.3Hz), 6.97(1H, dd, J=6.6, 7.3 Hz), 7.11(1H, dd, J=1.5, 8.1 Hz), 7.16(1H, d, J=7.3 Hz), 7.35-7.51 (5H, m), 7.94(2H, d, J=8.1 Hz), 9.12(1H, br.t, J=5.9 Hz), 9.63(1H, br.s)
IR(KBr)cm^{-1}: 3301, 1637, 1524, 1489, 1457, 1314, 1248, 752

Example 6

N-(2-aminophenyl)-4-[N-(4-methoxybenzoyl)aminomethyl]benzamide (Table 1: Compound 31)

[0078]

mp: 149-151 °C
^{1}H NMR(270MHz, DMSO-d_6) δ ppm: 3.82(3H, s), 4.53(2H, d, J=5.9 Hz), 4.88(2H, s), 6.59(1H, dd, J=7.3, 7.3Hz), 6.77(1H, d, J=8.1Hz), 6.94-7.00(1H, m), 7.02(2H, d, J=8.8 Hz), 7.16(1H, d, J=8.1 Hz), 7.43(2H, d, J=8.1 Hz), 7.89 (2H, d, J=8.8 Hz), 7.94(2H, d, J=8.1 Hz), 8.98(1H, br.t, J= 5.9 Hz), 9.61(1H, br.s)
IR(KBr)cm^{-1}: 3297, 1630, 1527, 1505, 1457, 1256, 1177, 1024,843, 749

Example 7

N-(2-aminophenyl)-4-[N-(3,4,5-trimethoxybenzoyl)aminomethyl]benzamide (Table 1: Compound 33)

[0079]

mp: 208-210 °C(dec.)
^{1}H NMR(270MHz, DMSO-d_6) δ ppm: 3.71(3H, s), 3.83(6H, s), 4.55(2H, d, J=5.9 Hz), 4.88(2H, br.s), 6.60(1H, dd, J=7.3, 8.1 Hz), 6.78(1H, d, J=8.1 Hz), 6.97(1H, dd, J=6.6, 8.1 Hz), 7.16(1H, d, J=8.1 Hz), 7.26(2H, s), 7.44(2H, d, J=8.1 Hz), 7.95(2H, d, J=8.8 Hz), 9.07(1H, t, J=5.9 Hz), 9.62(1H, br.s)
IR(KBr)cm^{-1}: 3267, 1635, 1582, 1457, 1237, 1132, 755

Example 8

N-(2-aminophenyl)-4-[N-[4-(N,N-dimethyl)aminobenzoyl]aminomethyl]benzamide (Table 1: Compound 36)

[0080]

mp: 216-219 °C(dec.)
^{1}H NMR(270MHz, DMSO-d_6) δ ppm: 2.98(6H, s), 4.51(2H, d, J=5.9 Hz), 4.88(2H, br.s), 6.60(1H, dd, J=8.1, 8.1 Hz), 6.71(2H, d, J=8.8 Hz), 6.97(1H, dd, J=7.3, 8.1 Hz), 7.16(1H, d, J=7.3 Hz), 7.41(2H, d, J=8.1 Hz), 7.78(2H, d, J=8.8 Hz), 7.93(2H, d, J=8.1 Hz), 8.77(1H, t, J=5.9 Hz), 9.63(1H, br.s).
IR(KBr)cm^{-1}: 3301, 1632, 1519, 1457, 1298, 754

Example 9

N-(2-aminophenyl)-4-[N-(4-trifluoromethylbenzoyl)aminomethyl]benzamide (Table 1: Compound 42)

[0081]

mp: 243-246 °C.
^{1}H NMR(270MHz, DMSO-d_6) δ ppm: 4.58(2H, d, J=5.9 Hz), 4.88(2H, br.s), 6.59(1H, dd, J=6.6, 7.3Hz), 6.77(1H, d, J=8.1 Hz), 6.94(1H, dd, J=5.9, 6.6 Hz), 7.16(1H, d, J=8.1 Hz), 7.45(2H, d, J=8.1 Hz), 7.88(2H, d, J=8.8 Hz), 7.95(2H, d, J=8.1 Hz), 8.11(2H, d, J=8.1 Hz), 9.38(1H, t, J=5.9 Hz), 9.64(1H, br.s)
IR(KBr)cm^{-1}: 3301, 1640, 1549, 1523, 1458, 1334, 1162, 1120, 1070, 856, 750

Example 10

N-(2-aminophenyl)-4-[N-(4-carboxybenzoyl)aminomethyl]benzamide hydrochloride (Table 1: hydrochloride of Compound 45)

[0082]

mp: (amorphous).
^{1}H NMR(270MHz, DMSO-d_6) δ ppm: 4.58(2H, d, J=5.9 Hz), 7.29-7.37(3H, m), 7.49(3H, d, J=8.1 Hz), 8.02-8.06 (6H, m), 9.36(1H, t, J=5.9 Hz), 10.4(1H, br.s)

IR(KBr)cm^{-1}: 3432(br.), 1718, 1637, 1542, 1499, 1303(br.), 1116, 1018, 757

Example 11

N-(2-aminophenyl)-4-[N-(4-methoxycarbonylbenzoyl)aminomethyl]benzamide (Table 1: Compound 46)

[0083]

mp: 204-209 °C(dec.)
^{1}H NMR(270MHz, DMSO-d_6) δ ppm: 3.89(3H, s), 4.57(2H, d, J=5.9 Hz), 4.88(2H, br.s), 6.60(1H, dd, J=6.6, 7.3 Hz), 6.78(2H, d, J=7.3 Hz), 6.97(1H, ddd, J=1.5, 6.6, 7.3 Hz), 7.16(1H, d, J=7.3 Hz), 7.45(2H, d, J=8.1 Hz), 7.95 (2H, d, J=8.1 Hz), 8.03(2H, d, J=8.8 Hz), 8.07(2H, d, J=8.8 Hz), 9.35(1H, t, J=5.9 Hz), 9.64(1H, br.s)
IR(KBr)cm^{-1}: 3287(br.), 1721, 1634, 1281, 1113, 750, 703

Example 12

N-(2-aminophenyl)-4-(N- picolinoylaminomethyl)benzamide (Table 1: Compound 164)

[0084]

mp: 173-178 °C(dec.)
^{1}H NMR(270MHz, DMSO-d_6) δ ppm: 4.57(2H, d, J=6.6 Hz), 4.88(2H, br.s), 6.59(1H, dd, J=7.3, 8.1 Hz), 6.77(1H, d, J=8.1 Hz), 6.96(1H, dd, J=7.3, 8.1Hz), 7.16(1H, d, J=7.3 Hz), 7.44(2H, d, J=8.1 Hz), 7.60-7.65(1H, m), 7.93(2H, d, J=8.1 Hz), 7.98-8.08(2H, m), 8.67(1H, d, J=4.4 Hz), 9.45(1H, t, J=6.6 Hz), 9.61(1H, br s)
IR(KBr)cm^{-1}: 3330, 1656, 1634, 1523, 1456, 1294, 752

Example 13

N-(2-aminophenyl)-4-[N-(6-methylpicolinoyl)aminomethyl]benzamide (Table 1: Compound 169)

[0085]

mp: 172-173 °C
^{1}H NMR(270MHz, DMSO-d_6) δ ppm: 2.51(3H, s), 4.57(2H, d, J=6.6 Hz), 5.0(2H, br.s), 6.61(1H, dd, J=7.3, 8.1 Hz), 6.79(1H, d, J=7.3 Hz), 6.98(1H, dd, J=7.3, 8.1 Hz), 7.16(1H, d, J=7.3 Hz), 7.44(2H, d, J=8.1 Hz), 7.43-7.49(1H, m), 7.84-7.90(2H, m), 7.94(2H, d, J=8.1 Hz), 9.35(1H, t, J=5.9 Hz), 9.64(1H, br.s)
IR(KBr)cm^{-1}: 3331, 1675, 1634, 1594, 1523, 1454, 1307, 1292, 750

Example 14

N-(2-aminophenyl)-4-(N-nicotinoylaminomethyl)benzamide (Table 1: Compound 71)

[0086]

mp: 193-196 °C
^{1}H NMR(270MHz, DMSO-d_6) δ ppm: 4.58(2H, d), 4.88(2H, br.s), 6.60(1H, t), 6.78(1H, d), 6.97(1H, t), 7.16(1H, d), 7.46(2H, d), 7.53(1H, dd), 7.95(2H, d), 8.24(1H, ddd), 8.73(1H, dd), 9.07(1H, d), 9.32(1H, br.t), 9.63(1H, br.s)
IR(KBr)cm^{-1}: 3301, 1639, 1522, 1457, 1314, 749, 705

Example 15

N-(2-aminophenyl)-4-[N-(2-methylnicotinoyl)aminomethyl]benzamide (Table 1: Compound 132)

[0087]

mp: 191-194 °C(dec.)
^{1}H NMR(270MHz, DMSO-d_6) δ ppm: 2.53(3H, s), 4.53(2H, d, J=5.9 Hz), 4.88(2H, br.s), 6.60(1H, dd, J=6.6, 8.1 Hz), 6.78(1H, d, J=7.3 Hz), 6.97(1H, dd, J=7.3, 8.1 Hz), 7.17(1H, d, J=7.3 Hz), 7.29(1H, dd, J=5.1, 8.1 Hz), 7.47

(2H, d, J=8.1 Hz), 7.29(1H, dd, J=1.5, 8.1 Hz), 7.97(2H, d, J=8.1 Hz), 8.51(1H, dd, J=1.5, 5.1 Hz), 9.06(1H, t, J=5.9 Hz), 9.64(1H, s)
IR(KBr)cm^{-1}: 3261, 1642, 1523, 1310, 753

Example 16

N-(2-aminophenyl)-4-[N-(6-methylnicotinoyl)aminomethyl]benzamide (Table 1: Compound 134)

[0088]

mp: 186-190 °C(dec.)
^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 2.36(3H, s), 4.56(2H, d, J=5.9 Hz), 4.88(2H, s), 6.60(1H, dd, J=7.4, 7.8 Hz), 6.78(1H, d, J=7.8 Hz), 6.97(1H, dd, J=6.9, 6.9 Hz), 7.16(1H, d, J=7.4 Hz), 7.37(1H, d, J=8.3 Hz), 7.45(2H, d, J=8.3 Hz), 7.95(2H, d, J=8.3 Hz), 8.13(1H, dd, J=2.0, 8.3 Hz), 8.96(1H, s), 9.24(1H, t, J=5.9 Hz), 9.63(1H, br.s)
IR(KBr)cm^{-1}: 3302, 1636, 1602, 1523, 1489, 1457, 1313, 751

Example 17

N-(2-aminophenyl)-4-[N-(2-chloronicotinoyl)aminomethyl]benzamide (Table 1: Compound 145)

[0089]

mp: 176-178 °C(dec.)
^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 4.54(2H, t, J=5.9 Hz), 4.90(2H, br.s), 6.60(1H, ddd, J=1.5, 7.3, 7.3 Hz), 6.78 (1H d, J=8.1 Hz), 6.97(1H, ddd, J=1.5, 7.3, 7.3 Hz), 7.18(1H, d, J=8.1 Hz), 7.48-7.54(3H, m), 7.94-7.99(3H, m), 8.49(1H, dd, J=2.1, 5.1 Hz), 9.23(1H, br.t, J=5.9 Hz), 9.65(1H, br.s)
IR(KBr)cm^{-1}: 3264, 1649, 1524, 1400, 1309, 751

Example 18

N-(2-aminophenyl)-4-[N-(6-chloronicotinoyl)aminomethyl]benzamide (Table 1: Compound 147)

[0090]

mp: 205-208 °C(dec.)
^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 5.57(2H, d, J=5.9 Hz), 6.60(1H, dd, J=7.3, 7.3 Hz), 6.78(1H, d, J=8.1 Hz), 6.60(1H, dd, J=7.3, 8.1 Hz), 6.78(1H, d, J=8.1 Hz), 7.45(2H, d, J=8.1 Hz), 7.66(1H, d, J=8.8 Hz), 7.95(2H, d, J=8.1 Hz), 8.27-8.32(1H, m), 8.90(1H, d, J=2.1 Hz), 9.38(1H, t, J=5.9 Hz), 9.63(1H, s)
IR(KBr)cm^{-1}: 3318(br.), 2929, 1646, 1590, 1525, 1503, 1454, 1108, 745

Example 19

N-(2-aminophenyl)-4-(N-isonicotinoylaminomethyl)benzamide (Table 1: Compound 174)

[0091]

mp: 234-237 °C(dec.)
^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 4.57(2H, t, J=5.9 Hz), 4.88(2H, br.s), 6.59(1H, dd, J=6.6, 7.3 Hz), 6.78(1H, d, J=8.1 Hz), 6.96(1H, dd, J=7.3, 7.3 Hz), 7.16(1H, d, J=7.3 Hz), 7.45(2H, d, J=8.1 Hz), 7.81(2H, d, J=1.5, 4.4 Hz), 7.95(2H, d, J=8.1 Hz), 8.75(2H, d, J=6.6 Hz), 9.41(1H, t, J=5.9 Hz), 9.62(1H, br.s)
IR(KBr)cm^{-1}: 3298, 1646, 1550, 1525, 1457, 1304, 843, 760, 695

Example 20

N-(2-aminophenyl)-4-[N-(pyrazin-2-yl)carbonylaminomethyl]benzamide (Table 1: Compound 182)

[0092]

mp: 207 °C(dec.)
^{1}H NMR (270 MHz, DMSO-d_6) δ ppm: 4.58(2H, d, J=5.9 Hz), 4.88(2H, br.s), 6.59(1H, dd, J=7.3, 7.3Hz), 6.77(1H, d, J=8.1Hz), 6.94(1H, ddd, J=1.5, 7.3, 8.1 Hz), 7.15(1H, d, J=7.3 Hz), 7.45(2H, d, J=8.1 Hz), 7.93(2H, d, J=8.1 Hz), 8.77(1H, d, J=1.5 Hz), 8.90(1H, d, J =2.1 Hz), 9.21(1H, s), 9.55-9.61(2H, m)
IR(KBr)cm^{-1}: 3368(br.), 1657, 1524, 1455, 1295, 1023, 751

Example 21

N-(2-aminophenyl)-4-[N-(thiophen-2-yl)carbonylaminomethyl]benzamide (Table 1: Compound 192)

[0093]

mp: 202-205 °C(dec.)
^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 4.52(2H, t, J=5.9 Hz), 4.88(2H, br.s), 6.60(1H, dd, J=6.6, 7.3Hz), 6.78(1H, d, J=8.1Hz), 6.97(1H, dd, J=7.3, 8.1 Hz), 7.15-7.18(2H, m), 7.43(2H ,d, J=8.1 Hz), 7.78(1H, d, J=4.4), 7.82(1H, d, J=3.7 Hz), 7.95(2H, d, J=8.1 Hz), 9.12(1H, br.t, J=5.9 Hz), 9.62(1H, br.s)
IR(KBr)cm^{-1}: 3306, 1633, 1523, 1456, 1297, 750, 716

Example 22

N-(2-aminophenyl)-4-[N-(furan-2-yl)carbonylaminomethyl]benzamide (Table 1: Compound 196)

[0094]

mp: 197 °C(dec.)
^{1}H NMR(270MHz. DMSO-d_6) δ ppm: 4.59(2H, d, J=6.6 Hz), 4.86(2H,br.s), 6.59(1H, dd, J=6.6, 6.6 Hz), 6.63(1H, dd, J=1.5, 3.6 Hz), 6.78(1H, d, J=8.1 Hz), 6.96(1H, dd, J=7.3, 6.6 Hz), 7.10-7.20(2H, m), 7.41(2H, d, J=8.1 Hz), 7.84(1H, s), 7.94(2H, d, J=8.1 Hz), 9.00(1H, br.t, J=5.9 Hz), 9.62(1H, s)
IR(KBr)cm^{-1}: 3245, 1651, 1573, 1545, 1323, 1241, 745

Example 23

N-(2-aminophenyl)-4-[N-(pyrrol-2-yl)carbonylaminomethyl]benzamide (Table 1: Compound 200)

[0095]

mp: 216-220 °C(dec.)
^{1}H NMR(270MHz, DMSO-d_6) δ ppm: 4.50(2H, d, J=5.9 Hz), 4.88(2H, br.s), 6.10(1H,dd, J=2.1, 5.9Hz), 6.59(1H, dd, J=7.3, 7.3 Hz), 6.77(1H, dd, J=1.5, 8.1 Hz), 6.84-6.88(2H, m), 6.97(1H, ddd, J=1.5, 7.3, 8.1 Hz), 7.16(1H, d, J=7.3 Hz), 7.41(2H, d, J=8.1 Hz), 7.94(2H, d, J=8.1 Hz), 8.62(1H, br.t, J=5.9 Hz), 9.62(1H, br.s)
IR(KBr)cm^{-1}: 3275, 1655, 1584, 1534, 1458, 1316, 747

Example 24

N-(2-aminophenyl)-4-[N-(N'-methyl-1H-pyrrol-2-yl)carbonylaminomethyl]benzamide (Table 1: Compound 201)

[0096]

mp: 177-179 °C(dec.)
^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 3.84(3H, s), 4.46(2H, d, J=5.9 Hz), 4.88(2H, br.s), 6.03(1H, dd, J=2.1, 4.4 Hz), 6.59(1H, dd, J=8.1, 8.1 Hz), 6.77(1H, d, J=8.1Hz), 6.84-6.97(2H, m), 7.16(1H, d, J=7.3 Hz), 7.41(2H, d, J=8.1 Hz), 7.93(2H, d, J=8.1 Hz), 8.61(1H, t, J=5.9 Hz), 9.62(1H, br.s)

IR(KBr)cm^{-1}: 3325(br.), 1630, 1551, 1520, 1507, 1324, 1265, 1154, 740

Example 25

N-(2-aminophenyl)-4-[N-(isoxazol-5-yl)carbonylaminomethyl]benzamide (Table 1: Compound 203)

[0097]

mp: 183-185 °C(dec.)
^{1}H NMR(270 MHz. DMSO-d_6) δ ppm: 4.53(2H, d, J=6.6 Hz), 4.89(2H, br.s), 6.60(1H, dd, J=7.3, 7.3Hz), 6.78(1H, d, J=7.3Hz), 6.97(1H, dd, J=7.3, 8.1 Hz), 7.12(1H, d, J=2.1 Hz), 7.16(1H, d, J=8.1 Hz), 7.44(2H, d, J=8.1 Hz), 7.95 (2H, d, J=8.1 Hz), 8.76(1H, d, J=1.5 Hz), 9.61(1H, t, J=5.9 Hz), 9.64(1H, br.s)
IR(KBr)cm^{-1}: 3278(br.), 1636, 1576, 1522, 1458, 1220, 749

Example 26

N-(2-aminophenyl)-4-[N-(3-methylisothiazol-5-yl)carbonylaminomethyl]benzamide (Table 1: Compound 204)

[0098]

mp: 168-169 °C.
^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 2.47(3H, s), 4.54(2H, d, J=5.9Hz), 4.89(2H, br.s), 6.60(1H, dd, J=7.3, 7.3 Hz), 6.78(1H, d, J=7.3Hz), 6.97(1H, ddd, J=1.0, 7.3, 8.1 Hz), 7.17(1H, d, J=7.3 Hz), 7.44(2H, d, J=8.1 Hz), 7.73 (1H, s), 7.96(2H, d, J=8.1 Hz), 9.44(1H, t, J=5.9 Hz), 9.64(1H, br.s)
IR(KBr)cm^{-1}: 3310, 1637, 1503, 1294, 751

Example 27

N-(2-aminophenyl)-4-[N-(imidazol-4-yl)carbonylaminomethyl]benzamide (Table 1: Compound 205)

[0099]

mp: (amorphous).
^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 4.49(2H, d, J=6.4 Hz), 4.87(2H, br.s), 6.59(1H, dd, J=6.9, 6.9Hz), 6.77(1H, d, J=6.9 Hz), 6.96(1H, dd, J=7.4, 7.4 Hz), 7.16(1H, d, J=6.9 Hz), 7.41(2H, d, J=6.9Hz), 7.64(1H, br.s), 7.73(1H, br.s), 7.92(2H, d, J=6.9 Hz), 8.56(1H, br.t, J=6.4 Hz), 9.61(1H, s), 12.5(1H, br.s)
IR(KBr)cm^{-1}: 3278(br.), 1636, 1576, 1522, 1458, 1220,749

Example 28

N-(2-aminophenyl)-4-[N-(3-aminophenyl)acetylaminomethyl]benzamide (Table 1: Compound 23)

[0100]

mp: 171-176 °C
^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 4.34(2H, d, J=5.9 Hz), 5.24(4H, br.s), 6.48-6.63(4H,m), 6.78-6.81(1H, m), 6.94-7.00(2H, m), 7.18(1H, d, J=8.1 Hz), 7.34(2H, d, J=8.1 Hz), 7.92(2H, d, J=8.1 Hz), 8.50(1H, t, J=5.9Hz), 9.61 (1H, s)

Example 29

N-(2-aminophenyl)-4-[N-(pyridin-3-yl)acetylaminomethyl]benzamide (Table 1: Compound 74)

[0101]

mp: 127 °C
^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 3.84(2H, s), 4.40(2H, d, J=5.8 Hz), 7.15-7.29(3H, m), 7.37(1H, d, J=6.6 Hz), 7.43(2H, d, J=8.8 Hz), 7.96(1H, m), 7.98(2H, d, J=8.8 Hz), 8.40(1H, d, J=8.8 Hz), 8.79-8.87(3H, m), 10.20(1H, s)

Example 30

N-(2-aminophenyl)-4-[N-[3-(pyridin-3- yl)propionyl]aminomethyl]benzamide (Table 1: Compound 75)

[0102]

mp: 183-186 °C
^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 2.51(2H, t, J=7.3 Hz), 2.88(2H, d, J=7.3 Hz). 4.31(2H, d, J=5.9 Hz), 4.89 (2H, br.s), 6.60(1H, dd, J=7.3, 8.1 Hz), 6.78(1H, d, J=8.1Hz), 6.97(1H, ddd, J=1.5, 7.3, 8.1 Hz), 7.16(1H, d, J=8.1 Hz), 7.23(2H, d, J=8.8 Hz), 7.28-7.33(1H, m), 7.63(1H, d, J=8.1 Hz), 7.89(2H, d, J=8.1 Hz), 8.41-8.45(3H, m), 9.62 (1H, br.s)
IR(KBr)cm^{-1}: 3407, 3313, 1640, 1552, 1522, 1456, 1309, 746, 717

Example 31

N-(2-aminophenyl)-4-[N-[4-(pyridin-3-yl)-1,4-dioxobutyl]aminomethyl]benzamide (Table 1: Compound 99)

[0103]

mp: 145-147 °C(dec.)
^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 2.37-2.50(2H, m), 2.62-2.68(2H, m), 4.13(2H, s). 4.86(2H, s), 6.56-6.61(1H, m), 6.76-6.79(1H, m), 6.94-6.99(1H, m), 7.10-7.39(4H, m), 7.43-7.46(1H, m), 7.78(2H, d, J=8.1 Hz), 8.60-8.64(1H, m). 9.58(1H, s)
IR(KBr)cm^{-1}:3348, 1691, 1655, 1534, 1508, 1458, 1395, 1315, 1083, 746

Example 32

N-(2-aminophenyl)-4-[N-(5-chloropyridin-3-yl)oxyacetylaminomethyl]benzamide (Table 1: Compound 149)

[0104]

mp: 199-201 °C.
^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 4.43(2H, d, J=6.6 Hz), 4.75(2H, s), 4.87(2H, br. s), 6.60(1H, dd, J=7.3, 8.1 Hz), 6.78(1H, d, J=8.1 Hz), 6.97(1H, dd, J=7.3, 8.1 Hz), 7.16(1H, d, J=8.1 Hz), 7.37(2H, d, J=8.1 Hz), 7.59(1H, d, J=2.2 Hz), 7.93(2H, d, J=8.1 Hz), 8.25(1H, d, J=1.5 Hz), 8.81(1H, t, J=6.6 Hz), 9.64(1H, s)
IR(KBr)cm^{-1}:3288, 3058, 1675, 1633, 1523, 1457, 1314, 912, 755

Example 33

N-(2-amino-5-methoxyphenyl)-4-[N-(pyridin-3-yl)oxyacetylaminomethyl]benzamide (Table 1: Compound 166)

[0105]

mp: 141-144 °C
^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 3.66(3H, s), 4.43(2H, d, J=5.9 Hz), 4.49(2H, br.s), 4.68(2H, s), 6.62(1H, dd, J=2.9, 8.8 Hz), 6.75(1H, d, J=8.8 Hz), 6.91(1H, d, J=2.2 Hz), 7.37(4H, m), 7.92(2H, d, J=8.8 Hz), 8.21(1H, dd, J=1.5, 4.4 Hz), 8.35(1H, d, J=2.7 Hz), 8.81(1H, s), 9.65(1H, s)

Example 34

N-(2-aminophenyl)-4-[N-[3-(pyridin-3-yl)-1,3-dioxopropyl]aminomethyl]benzamide (Table 1: Compound 97)

[0106]

mp: 204-206 °C
^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 4.08(4/3H, s), 4.39(4/3H, d, J=5.9 Hz), 4.49(2/3H, d, J=5.9 Hz), 4.90(2H, br.s), 5.93(1/3H, s), 6.60(1H, t, J=7.3 Hz), 6.78(1H, d, J=8.1 Hz), 6.97(1H, t, J=7.3 Hz), 7.16(1H, d, J=7.3 Hz), 7.3-7.7(3H, m), 7.8-8.4(3H, m), 8.6-9.2(3H, m), 9.64(1H, s), 14.74(1/3H, s). (2:1 equilibrium mixture)

IR(KBr)cm^{-1}: 3282, 1690, 1645, 1527, 1421, 1314, 1217, 1028, 994, 911, 753, 701

Example 35

N-(2-aminophenyl)-4-[N-[N-(pyridin-3-yl)aminoacetyl]aminomethyl]benzamide (Table 1: Compound 95)

[0107]

mp: (amorphous)
^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 3.77(2H, d, J=6.6 Hz), 4.37(2H, d, J=5.9 Hz), 4.87(2H, br.s), 6.27(1H, t, J=5.9 Hz), 6.60(1H, dd, J=7.3, 7.3Hz), 6.78(1H, d, 7.3 Hz), 6.87(1H, d, J=8.1 Hz), 6.96(1H, dd, J=7.3, 8.1 Hz), 7.09(1H, d, J=4.4 Hz), 7.12(1H, d, J=4.4 Hz), 7.16(1H, d, J=8.1 Hz), 7.33(2H, d, J=8.8 Hz), 7.81(1H, d, J=4.4 Hz), 7.91(2H, d, J=7.3 Hz), 7.99(1H, d, J=2.9 Hz), 8.59(1H, br.t, J=5.1 Hz), 9.63(1H, br.s)
IR(KBr)cm^{-1}: 3350, 1658, 1525, 1502, 1314, 750

Example 36

N-(2-aminophenyl)-4-[N-(2-aminothiazol-4-yl)acetylaminomethyl]benzamide (Table 1: Compound 211)

[0108]

mp: (amorphous).
^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 3.34(2H, s), 4.35(2H, d, J=5.9 Hz), 4.87(2H, s), 6.25(1H, s), 6.59(1H, dd, J=7.3, 7.3 Hz), 6.78(1H, d, J=7.3 Hz), 6.87(2H, s), 6.96(1H, dd, J=7.3, 7.3 Hz), 7.16(1H, d, J=7.3 Hz), 7.37(2H, d, J=8.1 Hz), 7.93(2H, d, J=8.1 Hz), 8.44(1H, t, J=5.9 Hz), 9.62(1H, s)

Example 37

N-(2-aminophenyl)-4-[N-(quinolin-6-yl)carbonylaminomethyl]benzamide (Table 1: Compound 222)

[0109]

mp: 209-210 °C.
^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 4.62(2H, d, J=5.9 Hz), 4.88(2H, s), 6.60(1H, t, J=7.7 Hz), 6.78(1H, d, J=7.3 Hz), 6.95(1H, d, J=7.3 Hz), 7.17(1H, d, J=7.3 Hz), 7.49(2H, d, J=8.8 Hz), 7.62(1H, dd, J=4.4, 8.1 Hz), 7.96(2H, d, J=8.8 Hz), 8.10(1H, d, J=8.8 Hz), 8.23(1H, dd, J=2.2, 8.8 Hz), 8.38(1H, m), 8.49(1H, d, J=8.1 Hz), 8.58(1H, s), 8.99(1H, s), 9.64(1H, s)
IR(KBr)cm^{-1}:3301, 1640, 1614, 1545, 1496, 1312, 910, 853, 745

Example 38

N-(2-aminophenyl)-4-[N-(furo[3,2-b]pyridin-2-yl)carbonylaminomethyl]benzamide (Table 1: Compound 224)

[0110]

mp: 191 °C(dec.)
^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 4.58(2H, d, J=5.9 Hz), 4.88(2H, s), 6.57-6.62(1H, m), 6.76-6.79(1H, m), 6.93-6.99(1H, m), 7.15-7.25(1H, m), 7.45-7.52(3H, m), 7.74(1H, s), 7.95(2H, d, J=8.1 Hz), 8.13(1H, d, J=8.8 Hz), 8.63(1H, d, J=3.7 Hz), 9.54(1H, t, J=5.9 Hz), 9.64(1H, s)
IR(KBr)cm^{-1}: 3406, 1662, 1529, 1507, 1420, 1313, 1209, 1139, 1170, 1139, 924, 741

Example 39

N-(2-aminophenyl)-4-[N-(furo[2,3-c]pyridin-2-yl)carbonylaminomethyl]benzamide (Table 1: Compound 225)

[0111]

mp: 210 °C(dec.)

^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 4.58(2H, J=6.6Hz), 4.87(2H, s), 6.57-6.62(1H, m), 6.76-6.79(1H, m), 6.93-6.99(1H, m), 7.14-7.17(1H, m), 7.47(2H, d, J=8.1 Hz), 7.66(1H, s), 7.82(1H, d, J=4.4 Hz), 7.96(2H, d, J=8.1 Hz), 8.48(1H, d, J=5.1 Hz), 9.06(1H, s), 9.60-9.64(2H, m)
IR(KBr)cm^{-1}: 3320, 1653, 1632, 1598, 1457, 1424, 1308, 1187, 1033, 853, 749

Example 40

N-(2-aminophenyl)-4-[N-(pyridin-3-yl)oxyacetyl-N-[3-(pyridin-3-yl)propyl]aminomethyl]benzamide (Table 1: Compound 91)

[0112]

mp: (amorphous)
^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 1.77-1.93(2H, m), 2.50-2.63(2H, m), 3.16-3.30(2H, m), 4.63(1.2H, s), 4.71 (0.8H, s), 4.88(1.2H, s), 4.95(0.8H, s), 5.05(2H, s), 6.57-6.63(1H, m), 6.77-6.79(1H, m), 6.94-7.00(1H, m), 7.11-7.42(5H, m), 7.58-7.64(1H, m), 7.92-8.02(2H, m), 8.15-8.43(5H, m), 9.65(0.6H, s), 9.69(0.4H, s)(a mixture of rotational isomers)

Example 41

N-(2-aminophenyl)-4-[N-methyl-N-(pyridin-3-yl)oxyacetyl]aminomethylbenzamide (Table 1: Compound 92)

[0113]

mp: 117-120 °C
^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 2.84 and 2.99(total 3H, s), 4.60 and 4.69(total 2H, s), 4.90(2H, br.s), 4.99 and 5.08(total 2H, s), 6.60(1H, dd, J=7.3, 8.1 Hz), 6.78(1H, d, J=8.1 Hz), 6.97(1H, dd, J=7.3, 7.3 Hz), 7.16(1H, d, J=7.3 Hz), 7.30-7.43(4H, m), 7.95 and 8.01(total 2H, d, J=8.1 Hz), 8.17(1H, d, J=4.4 Hz), 8.31(1H, d, J=2.9 Hz), 9.65 and 9.68(total 1H, br.s) (a mixture of rotational isomers)
IR(KBr)cm^{-1}:3298, 1665, 1501, 1425, 1310, 1276, 1254, 1078, 799, 746, 703

Example 42

Preparation of N-(2-aminophenyl)-4-[N-(pyridin-3-yl)oxamoylaminomethyl]benzamide (Table 1: Compound 94)

[0114]

(42-1) Ethyl N-(pyridin-3-yl)oxamate (388 mg, 2mmol) and 638 mg of the compound from the process(1-4) (2 mmol) were dissolved in ethanol, and the mixture was heated with stirring at 40 to 50 °C for 2.5 hours. The precipitated crystals were collected by filtration and washed with 2 mL of ethanol and 3 mL of diethyl ether. The crystals were dried to give 724 mg of N-[2-(N-tert-butoxycarbonyl)aminophenyl]-4-[N-(pyridin-3-yl)oxamoylaminomethyl] benzamide (Yield: 74 %).

^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 1.44(9H, s), 4.49(2H, d, J=5.9 Hz), 7.10-7.30(2H, m), 7.35-7.57(5H, m), 7.93(2H, d, J=8.1 Hz), 8.21(1H, br.d, J=5.1 Hz), 8.35(1H, dd, J=1.5, 5.1 Hz), 8.68(1H, br.s), 9.00(1H, d, J=2.9 Hz), 9.70(1H, t, J=5.9 Hz), 9.82(1H, s), 10.98(1H, br.s)

(42-2) To a suspension of 720 mg of the compound from the process (42-1) in 8 mL of methanol was added 8 mL of 4N hydrochloric acid-dioxane solution. After stirring for 3 hours, the mixture was poured into a diluted sodium hydroxide aq. to be basified, and the precipitated crystals were collected by filtration. The crystals were recrystallized from THF/methanol = 1:1, to give 280 mg of the desired product.

mp: 254-258 °C(dec.)
^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 4.67(2H, d, J=5.9 Hz), 4.89(2H, br.s), 6.59(1H, dd, J=7.3 Hz), 6.77 (1H, d, J=8.1 Hz), 6.97(1H, dd, J=6.6, 7.3 Hz), 7.16(1H, d, J=8.1 Hz), 7.38-7.44(1H, m), 7.43(2H, d, J=8.1 Hz), 7.95(2H, d, J=8.1 Hz), 8.18-8.24 (1H, m), 8.34(1H, dd, J=1.5, 4.4 Hz), 9.00(1H, d, J=2.1 Hz), 9.63(1H, s), 9.69 (1H, br.t, J=6.6 Hz), 10.97(1H, br.s)
IR(KBr.cm^{-1}):3312, 3270, 1663, 1636, 1521, 1312, 1296, 1019

Example 43

Preparation of N-(2-aminophenyl)-4-[N-(pyridin-3-yl)oxyacetylaminomethyl]benzamide (Table 1: Compound 61)

[0115]

(43-1) To a suspension of 0.22 g of sodium hydride (60 % oil dispersion, 5.5 mmol) in 2mL of DMF was added dropwise a solution of 0.48 g of 3-hydroxypyridine (5.0mmol) in 2mL of DMF at room temperature, and the mixture was stirred for an hour. The resulting brown solution was ice-cooled, 0.81 mL of tert-butyl bromoacetate (5.5 mmol) was added, and the mixture was stirred under ice-cooling for an hour followed by stirring at room temperature for 2 hours. After addition of water, the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried and evaporated. The residue was purified by column chromatography on silica gel (eluent: chloroform: ethyl acetate = 5:1), to give 0.34 g of tert-butyl 3-pyridyloxyacetate (Yield: 32.5 %) as a clear oil.

^{1}H NMR(270 MHz, $CDCl_3$) δ ppm: 1.49(9H, s), 4.56(2H, s), 7.18-7.24(2H, m), 8.26(1H, dd, J=1.5, 3.6 Hz), 8.32(1H, d, J=2.9 Hz)

(43-2) To a solution of 0.14 g of the compound from the process (43-1) (0.67 mmol) in 2 mL of dichloromethane was added 2 mL of trifluoroacetic acid, and the solution was stirred at room temperature for 3 hours. After evaporation, diisopropyl ether was added, and the precipitated solid was collected by filtration and dried to give 0.15 g of 3-pyridyloxyacetic acid trifluoroacetate (Yield: 83.8 %) as a light yellow solid.

^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 4.86(2H, s), 7.57(1H, dd, J=4.4, 8.1 Hz), 7.67(1H, ddd, J=1.5, 1.5, 8.8 Hz), 8.31(1H, d, J=5.1 Hz), 8.46(1H, d, J=2.1 Hz), 13.00(1H, br.s)

(43-3) To a suspension of 100 mg of the compound from the process (43-2) (0.37 mmol) and 255 mg of the compound from Example 1, the process (1-4) (0.75 mmol) in 5 mL of dichloromethane was added 0.14 mL of triethylamine (1.0 mmol), and the mixture was cooled with ice. Under ice-cooling, to the mixture was added a solution of 140 mg of 2-chloro-1,3-dimethylimidazolinium chloride (0.83 mmol) in 6 mL of dichloromethane, and the mixture was warmed to room temperature with stirring for 7 hours, and left at room temperature overnight. After adding water and saturated brine, the mixture was extracted with chloroform.

The organic layer was washed with saturated brine, dried and evaporated. The residue was purified by column chromatography on silica gel (eluent: ethyl acetate:methanol = 10:1) to give 0.37 g of N-[2-(N-tert-butoxycarbonyl)aminophenyl]-4-[N-(pyridin-3-yl)oxyacetylaminomethyl]benzamide (Yield: quantitative) as a clear oil.

^{1}H NMR(270 MHz, $CDCl_3$) δ ppm: 1.52(9H, s), 4.62(2H, s), 4.63(2H, d, J=7.3 Hz), 6.76(1H, br.s), 6.90-7.00 (1H, br.s), 7.15-7.35(5H, m), 7.40(2H, d, J=8.1 Hz), 7.82(1H, d, J=8.1 Hz), 7.95(2H, d, J=8.1 Hz), 8.32(1H, dd, J=2.1, 4.4 Hz), 8.37(1H, d, J=2.8 Hz), 9.20(1H, br.s)

(43-4) To a solution of 175 mg of the compound from the process (43-3) (0.37 mmol) in 2mL of dioxane and 2mL of methanol was added 2 mL of 4N hydrochloric acid-dioxane, and the mixture was stirred at room temperature for 2 hours. After adding saturated sodium bicarbonate aq., the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried and evaporated. To the residue was added methanol and diisopropyl ether, and the precipitated solid was collected by filtration and dried to give 90 mg of N-(2-aminophenyl)-4-[N-(pyridin-3-yl)oxyacetylaminomethyl]benzamide (Yield: 64.6 %) as an opalescent solid.

mp: 154-155 °C

^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 4.42(2H, d, J=5.9 Hz), 4.69(2H, s), 4.89(2H, br.s), 6.59(1H, dd, J=7.3, 8.1 Hz), 6.78(1H, d, J=8.1 Hz), 6.97(1H, dd, J=6.6, 7.3 Hz), 7.16(1H, d, J=7.3 Hz), 7.33-7.39(4H, m), 7.92(2H, d, J=8.1 Hz), 8.21(1H, dd, J=1.5, 4.4 Hz), 8.35(1H, d, J=2.9 Hz), 8.80(1H, br.t, J=5.9 Hz), 9.63(1H, br.s)

IR(KBr)cm^{-1}: 3307, 1672, 1631, 1523, 1456, 1429, 1269, 1231, 803, 756

Example 44

Preparation of N-(2-aminophenyl)-4-[N-(pyridin-3-yl)methoxycarbonylaminomethyl)benzamide (Table 1: Compound 82)

[0116]

(44-1) To a solution of 384 mg of 3-pyridinemethanol (3.52 mmol) in 5 mL of dry THF were added 523 mg of N,N'-carbonyldiimidazole (3.22 mmol) at room temperature. After stirring for an hour, to the mixture was added 1.0 g of the compound from Example 1, the process (1-4) (2.93 mmol) in 6 mL of dry THF.

After being left at room temperature overnight, to the mixture was added 100 mL of chloroform, and the mixture was washed with water (3 × 20 mL) and then saturated brine, and dried over anhydrous magnesium sulfate. After evaporating the solvent under reduced pressure, the residue was purified by column chromatography on silica gel

(eluent: chloroform:methanol = 30:1) to give 1.27 g of N-[2-(N-tert-butoxycarbonyl)aminophenyl]-4-[N-(pyridin-3-yl) methoxycarbonylaminomethyl]benzamide (Yield: quantitative) as an amorphous solid.

^{1}H NMR(270 MHz, $CDCl_3$) δ ppm: 1.51(9H, s), 4.45(2H, d, J=5.9 Hz), 5.16(1H, s), 7.10-7.50(7H, m), 7.70 (1H, d, J=8.1 Hz), 7.80(1H, d, J=7.3 Hz), 7.93(1H, d, J=8.1 Hz), 8.57(1H, d, J=4.4 Hz), 8.63(1H, s), 9.17(1H, s).

(44-2) The compound from the process (44-1)(1.2 g, 2.8 mmol) was dissolved in 10 mL of methanol. To the solution was added 20 mL of 4N-hydrochloric acid-dioxane. The mixture was stirred at room temperature for 1.5 hours, and then poured into diluted sodium-hydroxide aq. and extracted with chloroform (3 × 60 mL). The combined organic layer was washed twice with saturated brine, dried over anhydrous magnesium sulfate and concentrated to give 0.88 g of crystals, which were then recrystallized from 16 mL of ethanol, to give 668 mg of N-(2-aminophenyl)-4-[N-(pyridin-3-yl)methoxycarbonylaminomethyl]benzamide (Yield: 73 %).

mp: 159-160 °C

^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 4.28(2H, d, J=5.9 Hz), 4.86(2H, s), 5.10(2H, s), 6.60(1H, t, J=7.3 Hz), 6.78(1H, d, J=7 Hz), 6.97(1H, t, J=7 Hz), 7.17(1H, d, J=8 Hz), 7.30-7.50(3H, m), 7.78(1H, d, J=8 Hz), 7.93(2H, d, J=8 Hz), 8.53(1H, d, J=3.7 Hz), 8.59(1H, s), 9.61(1H, s).

IR(KBr)cm^{-1}: 3295, 1648, 1541, 1508, 1457, 1309, 1183, 742

[0117] As described in Example 44, the compounds of Examples 45 to 77 were prepared, each of whose melting point (mp), ^{1}H NMR data and/or IR data are shown below.

Example 45

N-(2-aminophenyl)-4-[N-(benzyloxycarbonyl)aminomethyl]benzamide (Table 1: Compound 11)

[0118]

mp: 174-178 °C

^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 4.28(2H, d, J=5.9 Hz), 4.89(2H, br.s), 5.06(2H, s), 6.59(1H, dd, J=7.3, 8.1 Hz), 6.78(1H, d, J=8.1 Hz), 6.97(1H, dd, J=7.3, 8.1 Hz), 7.16(1H, d, J=7.3 Hz), 7.30-7.40(6H, m), 7.93(3H, m), 9.63(1H, s).

IR(KBr)cm^{-1}: 3332, 1687, 1652, 1536, 1456, 1279, 747

Example 46

N-(2-aminophenyl)-4-[N-(4-(imidazol-1-yl)benzyl)oxycarbonylaminomethyl]benzamide (Table 1: Compound 47)

[0119]

mp: 195-198 °C

^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 4.29(2H, d, J=6.6 Hz), 4.88(2H, s), 5.10(2H, s), 6.60-6.63(1H, m), 6.78(1H, d, J=8.1Hz), 6.97(1H, t, J=7.3Hz), 7.11(1H, s), 7.16(1H, d, J=7.3 Hz), 7.37(2H, d, J=8.1 Hz), 7.49(2H, d, J=8.8 Hz), 7.66(2H, d, J=8.1 Hz), 7.74(1H, s), 7.92-7.96(3H, m), 8.25(1H, s), 9.62(1H, s)

Example 47

N-(2-aminophenyl)-4-[N-(pyridin-2-yl)methoxycarbonylaminomethyl]benzamide (Table 1: Compound 162)

[0120]

mp: 166-167 °C

^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 4.30(2H, d, J=5.9 Hz), 4.88(2H, br.s), 5.12(2H, s), 6.60(1H, dd, J=7.3, 8.1 Hz), 6.78(1H, d, J=8.1 Hz), 6.97(1H, ddd, J=1.5, 7.3, 8.1 Hz), 7.16(1H, d, J=7.3 Hz), 7.33(1H dd, J=3.7, 7.3 Hz), 7.40(3H, d, J=8.1 Hz), 7.83(1H, ddd, J=1.5, 7.3, 8.1 Hz), 7.94(2H, d, J=8.1 Hz), 8.03(1H, t, J=5.9 Hz), 8.55(1H, d, J=5.1 Hz), 9.62(1H, br.s)

IR(KBr)cm^{-1}: 3334, 1694, 1632, 1580, 1276, 755

Example 48

N-(2-aminophenyl)-4-[N-[2-(pyridin-2-yl)ethoxycarbonyl]aminomethyl]benzamide (Table 1: Compound 163)

[0121]

mp: 146-148 °C
^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 3.04(2H, t, J=6.6 Hz), 4.23(2H, d, J=5.9 Hz), 4.36(2H, t, J=6.6 Hz), 4.88(2H, br.s), 6.60(1H, dd, J=7.3, 8.1 Hz), 6.78(1H, d, J=8.1 Hz), 6.97(1H, dd, J=7.3, 8.1 Hz), 7.15-7.30(3H, m), 7.34(2H, d, J=8.1 Hz), 7.69 -7.77(2H, m), 7.92(2H, d, J=7.3 Hz), 8.50(1H, d, J=4.4 Hz), 9.62(1H, br.s)
IR(KBr)cm^{-1}: 3330, 1690, 1633, 1594, 1524, 1277, 760

Example 49

N-(2-aminophenyl)-4-[N-(6-methylpyridin-2-yl)methoxycarbonylaminomethyl]benzamide (Table 1: Compound 170)

[0122]

mp: 138 °C
^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 2.47(3H, s), 4.30(2H, d, J=5.9 Hz), 5.07(4H, s), 6.63(1H, t, J=8.1 Hz), 6.80 (1H, d, J=7.34), 6.98(1H, t, J=8.1 Hz), 7.18(3H, d, J=7.3 Hz), 7.40(2H, d, J=8.1 Hz), 7.71(1H, t, J=8.1 Hz), 7.94 (2H, d, J=8.1 Hz), 8.03(1H, t, J=5.9 Hz), 9.66(1H, s)
IR(KBr)cm^{-1}: 3335, 1693, 1634, 1259

Example 50

N-(2-aminophenyl)-4-[N-[2-(pyridin-3-yl)ethoxycarbonyl]aminomethyl]benzamide (Table 1: Compound 83)

[0123]

mp: 120-125 °C
^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 2.91(2H, t, J=6.6 Hz), 4.22(4H, t, J=6.6 Hz), 4.89(2H, s), 6.55-6.63(1H, m), 6.78(1H, dd, J=8.1, 1.5 Hz), 6.97(1H, t, J=6.6 Hz), 7.17(1H, d, J=6.6 Hz), 7.33(3H, d, J=8.1 Hz), 7.69(1H, d, J=8.1 Hz), 7.79(1H, t, J=6.6 Hz), 7.93(2H, d, J=8.0 Hz), 8.43-8.49(2H, m), 9.62(1H, s)
IR(KBr)cm^{-1}: 3234, 1705, 1655, 1260

Example 51

N-(2-aminophenyl)-4-[N-[3-(pyridin-3-yl)propyloxycarbonyl]aminomethyl]benzamide (Table 1: Compound 84)

[0124]

mp: 121-124 °C
^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 1.83-1.94(2H, m), 2.67(2H, t, J=7.3 Hz), 3.98(2H, t, J=6.6 Hz), 4.26(2H, d, J=5.9 Hz), 4.89(2H, br.s), 6.60(1H, dd, J=8.1, 8.1 Hz), 6.78(1H, d, J=7.3 Hz), 6.97(1H, ddd, J=1.5, 7.3, 8.1 Hz), 7.16(1H, d, J=8.1 Hz), 7.29-7.33(1H, m), 7.37(1H, d, J=8.1 Hz), 7.64(1H, d, J=8.1 Hz), 7.81(1H, dd, J=5.9, 6.6Hz), 7.94(2H, d, J=8.1 Hz), 8.40-8.44(2H,m), 9.63(1H, br.s)
IR(KBr)cm^{-1}: 3348, 1696, 1635, 1523, 1458, 1302, 1272, 1141, 1019, 754, 713

Example 52

N-(2-aminophenyl)-4-[N-(2-methylpyridin-3-yl)methoxycarbonylaminomethyl]benzamide (Table 1: Compound 133)

[0125]

mp: 164-165 °C
^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 2.49(3H, s), 4.28(2H, d, J=6.6 Hz), 4.89(2H, s), 5.10(2H, s), 6.60(1H, t, J=6.6 Hz), 6.78(1H, d, J=8.1 Hz), 6.90(1H, t, J=7.3 Hz), 7.17(1H, d, J=7.3 Hz), 7.21-7.26(1H, m), 7.37(2H, d, J=8.1 Hz),

7.68(1H, d, J=6.6 Hz), 7.92-8.00(3H, m), 8.39(1H, d, J=4.4 Hz), 9.62(1H, s)
IR(KBr)cm^{-1}: 3332, 1719, 1630, 1260

Example 53

N-(2-aminophenyl)-4-[N-(6-methylpyridin-3-yl)methoxycarbonylaminomethyl]benzamide (Table 1: Compound 135)

[0126]

mp: 164-165 °C
^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 2.46(3H, s), 4.27(2H, d, J=6.6Hz), 4.88(2H, s), 5.05(2H, s), 6.59(1H, dt, J=1.5, 8.1Hz), 6.78(1H, dd, J=1.5, 8.1Hz), 6.97(1H, dt, J=1.5, 7.3 Hz), 7.17(1H, d, J=7.3 Hz), 7.26(1H, d, J=8.1 Hz), 7.36(2H, d, J=8.1 Hz), 7.67(1H, dd, J=2.2, 8.1 Hz), 7.93(3H, d, J=8.1 Hz), 8.45(1H, d, J=1.5 Hz), 9.62(1H, s)
IR(KBr)cm^{-1}: 3293, 1701, 1632, 1260

Example 54

N-(2-aminophenyl)-4-[N-(2-chloropyridin-3-yl)methoxycarbonylaminomethyl]benzamide (Table 1: Compound 146)

[0127]

mp: (amorphous)
^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 4.30(2H, d, J=5.9 Hz), 5.00(2H, s), 5.13(2H, s), 6.61(1H, t, J=7.3 Hz), 6.79 (1H, dd, J=1.5, 8.1 Hz), 6.98(1H, dt, J=1.5, 7.3 Hz), 7.17(1H, d, J=6.6 Hz), 7.39(2H, d, J=8.8 Hz), 7.47-7.52(1H, m), 7.91-7.96(3H, m), 8.08(1H, t, J=5.9 Hz), 8.40(1H, dd, J=4.4, 1.5 Hz), 9.64(1H, s)
IR(KBr)cm^{-1}: 3340, 1702, 1632, 1273

Example 55

N-(2-aminophenyl)-4-[N-(6-chloropyridin-3-yl)methoxycarbonylaminomethyl]benzamide (Table 1: Compound 148)

[0128]

mp: 180-185 °C
^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 4.24(2H, d, J=5.9 Hz), 4.89(2H, br.s), 5.10(2H, s), 6.60(1H, t, J=7.3 Hz), 6.78(1H, d, J=8.1 Hz), 6.97(1H, dt, J=1.5, 8.1 Hz), 7.16(1H, d, J=6.6 Hz), 7.37(2H, d, J=8.1 Hz). 7.56(1H, d, J=8.1 Hz), 7.85-8.02(4H, m), 8.44(1H, d, J=2.2 Hz), 9.62(1H, s)
IR(KBr)cm^{-1}: 3346, 3282, 1696, 1533, 1271

Example 56

N-(2-aminophenyl)-4-[N-(pyridin-4-yl)methoxycarbonylaminomethyl]benzamide (Table 1: Compound 172)

[0129]

mp: 180-183 °C
^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 4.30(2H, d, J=6.6 Hz), 4.89(2H, s), 5.12(2H, s), 6.60(1H, dd, J=7.3, 7.3 Hz), 6.78(1H, dd, J=1.5, 7.3 Hz), 6.97(1H, ddd, J=1.5, 7.3, 8.1 Hz), 7.16(1H, d, J=7.3 Hz), 7.34(2H, d, J=5.9 Hz), 7.39 (2H, d, J=8.1 Hz), 7.94(2H, d, J=8.1 Hz), 8.09(1H, t, J=5.9 Hz), 8.57(1H, d), 9.64(1H, br.s)
IR(KBr)cm^{-1}: 3394, 3290, 1711, 1645, 1624, 1535, 1504, 1321, 1251, 1138, 1049, 763

Example 57

N-(2-aminophenyl)-4-[N-[2-(thiophen-3 yl)ethoxycarbonyl]aminomethyl]benzamide (Table 1: Compound 194)

[0130]

mp: (amorphous)

^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 2.90(2H, t, J=7.3 Hz), 4.17-4.26(4H, m), 4.89(2H, s), 6.60(1H, t, J=8.1 Hz), 6.78(1H, d, J=6.6 Hz), 6.97(1H, t, J=7.3 Hz), 7.06(1H, d, J=5.1 Hz), 7.17(1H, d, J=7.3 Hz), 7.26(1H, s), 7.36(2H, d, J=8.1Hz), 7.47(1H, t, J=2.2 Hz), 7.81(1H, t, J=5.9 Hz), 7.93(2H, d, J=8.1 Hz), 9.63(1H, s).
IR(KBr)cm^{-1}: 3314, 1716, 1638, 1252

Example 58

N-(2-aminophenyl)-4-[N-(3-phenyloxazol-5-yl)methoxycarbonylaminomethyl]benzamide (Table 1: Compound 202)

[0131]

mp: 192-195 °C
^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 4.30(2H, d, J=5.9 Hz), 4.89(.2H, s), 5.25(2H, s), 6.60(1H, t, J=6.6 Hz), 6.68 (1H, d, J=8.1 Hz), 6.94(1H, t, J=7.3 Hz), 7.09(1H, s), 7.16(1H, d, J=7.3 Hz), 7.39(2H, d, J=8.1Hz), 7.51(4H, d, J=2.2 Hz), 7.87-7.96(5H, m), 8.12(1H, t, J=5.9 Hz), 9.62(1H, s)
IR(KBr)cm^{-1}: 3292, 1718, 1630, 1262

Example 59

N-(2-aminophenyl)-4-[N-(thiazol-5-yl)methoxycarbonylaminomethyl]benzamide (Table 1: Compound 207)

[0132]

mp: 168-175 °C
^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 4.28(2H, d, J=5.9 Hz), 4.91(2H, br.s), 5.30(2H, s), 6.60(1H, dd, J=7.3, 7.3 Hz), 6.78(1H, d, J=8.1 Hz), 6.97(1H, dd, J=7.3, 8.1 Hz), 7.16(1H, d, J=7.3 Hz), 7.36(2H, d, J=8.1 Hz), 7.91-8.00 (4H, m), 9.09(1H, s), 9.63(1H, s)
IR(KBr)cm^{-1}: 3346(br.), 1697, 1636, 1525, 1456, 1271, 873, 753

Example 60

N-(2-aminophenyl)-4-[N-[2-(4-methylthiazol-5-yl)ethoxycarbonyl]aminomethyl]benzamide (Table 1: Compound 208)

[0133]

mp: 130-133 °C
^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 2.32(3H, s), 3.07(2H, t, J=5.9 Hz), 4.15(2H, t, J=5.9 Hz), 4.25(2H, d, J=6.6Hz), 4.89(2H, s), 6.60(1H, t, J=5.9Hz), 6.78(1H, dd, J=7.3, 1.5 Hz), 6.97(1H, dt, J=1.5, 7.3 Hz), 7.16(1H, d, J=8.1 Hz), 7.35(2H, d, J=8.1 Hz), 7.83(1H, t, J=5.9 Hz), 7.94(2H, d, J=8.1 Hz), 8.85(1H, s), 9.62(1H, s)
IR(KBr)cm^{-1}: 3350, 1691, 1635, 1270

Example 61

N-(2-aminophenyl)-4-[N-(1-methylpiperidin-3-yl)methoxycarbonylaminomethyl]benzamide (Table 1: Compound 216)

[0134]

mp: 130-135 °C
^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 1.49-1.78(3H, m), 1.83-2.01(3H, m), 2.30(3H, s), 2.85(2H, t), 3.74-3.94(2H, m), 4.25(2H, d, J=5.8 Hz), 6.55-6.62(3H, m), 6.78(1H, d, J=8.1 Hz), 6.97(1H, t, J=7.3 Hz), 7.16(1H, d, J=8.1 Hz), 7.37(2H, d, J=8.1 Hz), 7.79(1H, t, J=6.6 Hz), 7.93(2H, d, J=8.0 Hz), 9.66(1H, s)
IR(KBr)cm^{-1}: 3323, 2722, 1702, 1648, 1263

Example 62

N-(2-aminophenyl)-4-[N-(4-methylpiperazin-1-yl)methoxycarbonylaminomethyl]benzamide (Table 1: Compound 218)

[0135]

mp: (amorphous)
^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 1.73(2H, t, J=6.6 Hz), 2.36-2.63(13H, m), 4.00(2H, t, J=6.6 Hz), 4.30(2H, d, J=5.8 Hz), 6.55-6.63(4H, m), 6.78(1H, d, J=6.6 Hz), 6.97(1H, t, J=7.3 Hz), 7.16(1H, d, J=7.3 Hz), 7.37(2H, d, J=8.7 Hz), 7.73(1H, t, J=5.9 Hz), 7.94(2H, d, J=8.0 Hz), 9.66(1H, s)
IR(KBr)cm^{-1}: 3341, 2706, 1701, 1262

Example 63

N-(2-aminophenyl)-4-[N-(tetrahydrofuran-3-yl)methoxycarbonylaminomethyl]benzamide (Table 1: Compound 212)

[0136]

mp: (amorphous)
^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 1.50-1.60(1H, m), 1.88-2.00(1H, m), 2.44-2.54(1H, m), 3.41-3.47(1H, m), 3.56-3.77(3H, m), 3.85-4.04(2H, m), 4.25(2H, d, J=5.9 Hz), 4.89(2H, s), 6.60(1H, dd, J=7.3, 7.3 Hz), 6.78(1H, d, J=8.1 Hz), 6.97(1H, dd, J=7.3, 8.1 Hz), 7.17(1H, d, J=8.1 Hz), 7.37(2H, d, J=8.1 Hz), 7.81(1H, t, J=5.9 Hz), 7.94 (2H, d, J=8.1 Hz), 9.62(1H, br.s)
IR(KBr)cm^{-1}: 3349, 1695, 1635, 1523, 1457, 1259, 754

Example 64

N-(2-aminophenyl)-4-[N-(phenoxycarbonyl)aminomethyl]benzamide (Table 1: Compound 12)

[0137]

mp: 174-175 °C
^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 4.36(2H, d, J=5.9 Hz), 4.90(2H, br.s), 6.60(1H, dd, J=7.3, 7.3 Hz), 6.77(1H, dd, J=7.3, 7.3 Hz), 6.98(1H, ddd, J=1.5, 7.3, 7.3 Hz), 7.05-7.24(4H, m), 7.39-7.46(4H, m), 7.97(2H, d, J=8.1 Hz), 8.41(1H, t, J=5.9 Hz), 9.65(1H, br.s)
IR(KBr)cm^{-1}: 3443, 3362, 3313, 1732, 1706, 1636, 1527, 1493, 1458, 1305, 1217, 748

Example 65

N-(2-aminophenyl)-4-[N-(pyridin-3-yl)oxycarbonylaminomethyl]benzamide (Table 1: Compound 81)

[0138]

mp: 209 °C(dec.)
^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 4.38(2H, d, J=6.6 Hz), 4.90(2H, br.s), 6.55-6.63(1H, m), 6.78(1H, d, J=8.1 Hz), 7.00(1H, dd, J=7.3, 7.3 Hz), 7.17(1H, d, J=8.8 Hz), 7.37-7.47(3H, m), 7.64(1H, d, J=8.8 Hz), 7.97(2H, d, J=8.1 Hz), 8.43(2H, d, J=3.1 Hz), 8.59(1H, t, J=5.9 Hz), 9.66(1H, br.s)

Example 66

N-(2-amino-5-fluorophenyl)-4-[N-(pyridin-3-yl)methoxycarbonylaminomethyl]benzamide (Table 1: Compound 109)

[0139]

mp: 160-162 °C
^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 4.28(2H, d, J=6.6 Hz), 4.81(2H, s), 5.10(2H, s), 6.70-6.90(2H, m), 7.10-8.00 (8H, m), 8.53(1H, d, J=3.6 Hz), 8.59(1H, s), 9.61(1H, s)
IR(KBr)cm^{-1}:3269, 1716, 1638, 1488, 1436, 1247, 1141, 1043, 744

Example 67

N-(2-aminophenyl)-4-[N-(2-aminophenyl)methoxycarbonylaminomethyl]benzamide (Table 1: Compound 51)

[0140]

mp: 149-151 °C(dec.)
^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 4.28(2H, d, J=5.9 Hz), 4.88(2H, s), 4.96(2H, s), 5.06(2H, s), 6.53(1H, dd, J=7.3, 7.3 Hz), 6.56-6.67(2H, m), 6.78(1H, dd, J=1.5, 8.1 Hz), 6.93-7.12(3H, m), 7.16(1H, d, J=6.6 Hz), 7.38(2H, d, J=8.1 Hz), 7.86(1H, t-like, J=5.9 Hz), 7.93(2H, d, J=8.1 Hz), 9.61(1H, s)
IR(KBr)cm^{-1}:3336, 1685, 1632, 1527, 1276, 748

Example 68

N-(2-aminophenyl)-4-[N-(quinuclidin-3-yl)oxycarbonylaminomethyl]benzamide (Table 1: Compound 219)

[0141]

mp: (amorphous)
^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 1.30-1.90(4H, m), 1.90(1H, br.s), 2.45-2.80(6H, m), 3.04-3.13(1H, m), 4.15 (2H, d, J=5.9 Hz), 4.55-4.60(1H, m), 4.88(2H, br.s), 6.60(1H, ddd, J=1.5, 7.3, 7.3 Hz), 6.78(1H, d, J=8.1 Hz), 6.97 (1H, ddd, J=1.5, 7.3, 7.3 Hz), 7.17(1H, d, J=6.6 Hz), 7.37(2H, d, J=8.1 Hz), 7.78(1H, t, J=5.9 Hz), 7.94(1H, d, J=7.3 Hz), 9.62(1H, s)
IR(KBr)cm^{-1}:3328, 2942, 1700, 1648, 1504, 1259, 749

Example 69

N-(2-aminophenyl)-4-[N-(3-aminophenyl)methoxycarbonylaminomethyl]benzamide (Table 1: Compound 52)

[0142]

mp: 149-153 °C(dec.)
^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 4.27(2H, d, J=5.9 Hz), 4.88 and 4.89(total 4H, each br.s), 5.08(2H, s), 6.47-6.63(3H, m), 6.78(1H, d, J=8.1 Hz), 6.94-7.02(2H, m), 7.15(1H, dd, J=7.3, 8.8 Hz), 7.37(2H, d, J=8.1 Hz), 7.84(1H, t, J=5.9 Hz), 7.93(2H, d, J=8.8 Hz), 9.61(1H, br.s)
IR.(KBr)cm^{-1}:3367, 1682, 1632, 1523, 1457, 1261, 754

Example 70

N-(2-aminophenyl)-4-[N-(1-methylimidazol-5-yl)methoxycarbonylaminomethyl]benzamide (Table 1: Compound 209)

[0143]

mp: 162-165 °C(dec.)
^{1}H NMR(270 MHz, DMSO-d6) δ ppm: 3.62(3H, s), 4.27(2H, d, J=5.9 Hz), 4.91(2H, br.s), 5.05(2H, s), 6.60(1H, dd, J=7.3, 7.3 Hz), 6.78(1H, d, J=8.1 Hz), 6.95-7.00(2H, m), 7.16(1H, d, J=7.3 Hz), 7.36(2H, d, J=8.1 Hz), 7.63(1H, s), 7.87-7.95(3H, m), 9.64(1H,br.s)
IR(KBr)cm^{-1}:3293, 1688, 1651, 1534, 1506, 1259, 1121, 1043, 748

Example 71

N-(2-amino-4-chlorophenyl)-4-[N-(pyridin-3-yl)methoxycarbonylaminomethyl]benzamide (Table 1: Compound 111)

[0144]

mp: 167-170 °C
^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 4.28(2H, d, J=5.9 Hz), 5.10(2H, s), 5.21(2H, s), 6.72(1H, dd, J=2.2, 8.1 Hz), 6.81(1H, d, J=2.2 Hz), 7.16(1H, d, J=8.1 Hz), 7.37(2H, d, J=8.1 Hz), 7.78(1H, d, J=8.1 Hz), 7.92(2H, d, J=8.1 Hz),

8.53(1H, d, J=4.4 Hz), 8.59(1H, s), 9.60(1H, s)
IR(KBr)cm^{-1}: 3347, 3062, 2931, 1653, 1576, 1505, 1456, 1428, 1301, 1232, 1114, 1070, 1019

Example 72

N-(2-aminophenyl)-4-[N-(5-methoxypyridin-3-yl)methoxycarbonylaminomethyl]benzamide (Table 1: Compound 152)

[0145]

mp: 169-170 °C
^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 3.83(3H, s), 4.29(2H, d, J=6.6 Hz), 4.87(2H, s), 5.09(2H, s), 6.57-6.62(1H, m), 6.76-6.79(1H, m), 6.94-6.99(1H, m), 7.14-7.18(1H, m), 7.36-7.39(3H, m), 7.91-7.99(3H, m), 8.19-8.30(2H, m), 9.63(1H, s)
IR(KBr)cm^{-1}:3330, 1694, 1633, 1524, 1457, 1298, 1269, 1045, 760

Example 73

N-(2-aminophenyl)-4-[N-(pyrazin-2 yl)methoxycarbonylaminomethyl]benzamide (Table 1: Compound 183)

[0146]

mp: 182 °C
^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 4.30(2H, d, J=6.6 Hz), 4.88(2H, br.s), 5.20(2H, s), 6.72(1H, dd, J=7.3, 8.1 Hz), 6.78(1H, d, J=8.1 Hz), 6.97(1H, dd, J=6.6, 8.1Hz), 7.16(1H, d, J=7.3 Hz), 7.39(2H, d, J=8.8 Hz), 7.94(2H, d, J=8.8 Hz), 8.08(1H, t-like, J=6.6 Hz), 8.53(1H, s), 8.65(1H, s), 8.68(1H, s), 9.63(1H, s)
IR(KBr)cm^{-1}:3266, 1709, 1632, 1535, 1508, 1284, 1055, 1022, 744

Example 74

N-(2-amino-5-methoxyphenyl)-4-[N-(pyridin-3-yl)methoxycarbonylaminomethyl]benzamide (Table 1: Compound 113)

[0147]

mp: 141-143 °C
^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 3.66(3H, s), 4.29(2H, d, J=5.9 Hz), 4.51(2H, br.s), 5.10(2H, s), 6.63(1H, dd, J=2.9, 8.8 Hz), 6.74(1H, d, J=8.8 Hz), 6.91(1H, d, J=2.2 Hz), 7.38(2H, d, J=8.8 Hz), 7.41(1H, s), 7.79(1H, d, J=8.1 Hz), 7.92(2H, d, J=8.1 Hz), 7.98(1H, t, J=5.9 Hz), 8.54(1H, d, J=3.7 Hz), 8.60(1H, s), 9.65(1H, s)

Example 75

N-(2-aminophenyl)-4-[N-(pyridin-3-yl)methyl-N-(pyridin-3-yl)methoxycarbonylaminomethyl]benzamide (Table 1: Compound 108)

[0148]

mp: (amorphous)
^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 4.50(2H, s), 4.56(2H, s), 4.87(2H, s), 5.21(2H, s), 6.60(1H, t, J=7.7 Hz), 6.78 (1H, d, J=7.3 Hz), 6.97(1H, d, J=7.3 Hz), 7.17(1H, d, J=7.3 Hz), 7.20-7.50(4H, m), 7.60-8.00(4H, m), 8.40-8.60 (4H, m), 9.65(1H, s)
IR(KBr)cm^{-1}: 3268; 1700, 1504, 1246, 1120, 940, 714

Example 76

N-(2-aminophenyl)-4-[N-[3-(pyridin-3-yl)propyl]-N-(pyridin-3-yl)methoxycarbonyloaminomethyl]benzamide (Table 1: Compound 112)

[0149]

mp: (amorphous)
^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 1.75-1.90(2H, m), 2.48-2.62(2H, m), 3.20-3.36(2H, m), 4.55(2H, s), 4.89 (2H, s), 5.16(2H, s), 6.57-6.63(1H, m), 6.76-6.80 (1H, m), 6.94-6.99(1H, m), 7.14-7.17(1H, m), 7.32-7.74(6H, m), 7.94(2H, d, J=8.1Hz), 8.30-8.65(4H, m), 9.64(1H, s)

Example 77

N-(2-aminophenyl)-4-[N-[2-(pyridin-3-yl)ethoxycarbonyl]amino]benzamide (Table 1: Compound 116)

[0150]

mp: (amorphous)
^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 3.00(2H, t, J=6.6 Hz), 4.37(2H, t, J=6.6 Hz), 4.87(2H, br.s), 6.60(1H, t, J=7.3 Hz), 6.97(1H, t, J=7.3 Hz), 7.15(1H, d, J=7.3 Hz), 7.36(1H, dd, J=4.4, 8.1 Hz), 7.56(2H, d, J=8.8 Hz), 7.92(2H, d, J=8.8 Hz), 8.46(1H, d, J=4.4 Hz), 8.54(1H, d, J=2.2 Hz), 9.95(1H, s)
IR(KBr)cm^{-1}:3285, 1695, 1519, 1315, 1233, 1079

Example 78

Preparation of N-(2-aminophenyl)-4-[N-(pyridin-3-yl)methoxythiocarbonylaminomethyl]benzamide (Table 1: Compound 86)

[0151]

(78-1) To a solution of 20 mg of 3-pyridinemethanol (0.18 mmol) in 5 mL of dry THF were added 30 mg of N,N'-thiocarbonyldiimidazole (0.16 mmol) at room temperature. After stirring overnight, to the mixture were added 50 mg of the compound from Example 1, the process (1-4) (0.14 mmol).

After leaving at room temperature overnight, to the solution was added 100 mL of chloroform, and the solution was washed with water (3 × 20 mL) and then saturated brine, and dried over anhydrous magnesium sulfate. After evaporation, the residue was purified by column chromatography on silica gel(eluent: chloroform:methanol = 30:1) to give 70 mg of N-[2-(N-tert-butoxycarbonyl)aminophenyl]-4-[N-(pyridin-3-yl)methoxythiocarbonylaminomethyl]benzamide (Yield: 88 %) as amorphous.

^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 1.45(9H, s), 4.73(2H, d, J=5.9 Hz), 5.52(2H, s), 6.73-7.33(3H, m), 7.35-7.43(2H, m), 7.58-7.95(5H, m), 8.14-8.65(3H, m), 9.80(1H, s), 9.91(1H, t)

(78-2) To a solution of 50 mg of the compound from the process (78-1) (0.10 mmol) in 3 mL of methanol was added 3 mL of 4N hydrochloric acid-dioxane, and the mixture was stirred at room temperature for 1.5 hours. The mixture was poured into diluted sodium hydroxide aq. to neutralize the residual hydrochloric acid, and then was extracted with chloroform (3 × 10 mL). The organic layer was washed twice with saturated brine, dried over anhydrous magnesium sulfate and concentrated to give 34 mg of N-(2-aminophenyl)-4-(N-(pyridin-3-yl)methoxythiocarbonylaminomethyl]benzamide (Yield: 87 %).

mp: 154-156 °C(dec.)

^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 4.73(2H, d, J=5.9 Hz), 4.88(2H, s), 5.52(2H, s), 6.60(1H, t, J=7.3 Hz), 6.77(1H, d, J=8.1 Hz), 6.96(1H, t, J=8.1 Hz), 7.16(1H, d, J=7.3 Hz), 7.29-7.41(3H, m), 7.83-7.95(3H, m), 8.50-8.56 (1H, m), 8.65(1H, s), 9.62(1H, s), 9.93(1H, s)

IR(KBr)cm^{-1}:3204, 3035, 1631, 1523, 1456, 1289, 1191, 920, 753

Example 79

Preparation of N-(2-aminophenyl)-4-[N'-(pyridin-3-ylmethyl)ureidomethyl]benzamide (Table 1: Compound 88)

[0152]

(79-1) To a solution of 0.28 g of 3-picolylamine (2.6 mmol) in 10 mL of THF was added 0.42 g of N,N'-carbonyldiimidazole (2.4 mmol) at roomtemperature, and the mixture was stirred for an hour. To the solution was added 0.58 g of the compound from Example 1, the process (1-4) (1.8 mmol) at room temperature, and the solution was stirred for 3 hours and then left overnight.

After diluting with water, the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried and evaporated. The residue was purified by column chromatography on silica gel (eluent: ethyl acetate:methanol = 10:1) to give 0.77 g of N-[2-(N-tert-butoxycarbonyl)amino]phenyl-4-[N'-(pyridin-3-ylmethyl)ureidomethyl]benzamide (Yield: 90 %) as a white amorphous solid.

^{1}H NMR(270 MHz, $CDCl_3$) δ ppm: 1.46(9H, s), 4.20(2H, d, J=5.1 Hz), 4.28(2H, d, J=4.3 Hz),6.10-6.30(2H, m), 7.00-7.25(4H, m), 7.33(1H, d, J=7.3 Hz), 7.49-7.54(2H, m), 7.58-7.64(3H, m), 7.75(1H, s), 8.28(1H, br.s), 8.39 (1H, d, J=5.1 Hz), 9.65 (1H, br.s)

(79-2) To a solution of 0.63 g of the compound from the process (79-1)(1.32 mmol) in 4 mL of dioxane and 2 mL of methanol was added 4 mL of 4N hydrochloride-dioxane, and the mixture was stirred at room temperature for 2 hours. After adding saturated sodium bicarbonate aq., the mixture was extracted with ethyl acetate-methyl ethyl ketone. The organic layer was washed with saturated brine, dried and evaporated. The residue was washed with diisopropyl ether to give 0.37 g of N-(2-aminophenyl)-4-[N'-(pyridin-3-ylmethyl)ureidomethyl]benzamide (Yield: 74.7 %) as a brown solid.

mp: 167-175 °C

^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 4.27(2H, d, J=5.9 Hz), 4.31(2H, d, J=5.9 Hz), 4.89(2H, br.s), 6.57-6.63 (3H, m), 6.78(1H, d, J=8.1 Hz), 6.97(1H, dd, J=7.3, 8.1 Hz), 7.17(1H, d, J=7.3 Hz), 7.32-7.38(3H, m), 7.66(1H, d, J=8.1 Hz), 7.93(2H, d, J=8.1 Hz), 8.44(1H, d, J=5.1 Hz), 8.49(1H, d, J=2.1 Hz), 9.63(1H, br.s)

IR(KBr)cm^{-1}: 3344, 3241, 1645, 1560, 1527, 1505, 1283, 751, 708

[0153] As described in Example 79, the compounds of Examples 80 to 84 were prepared, each of whose melting point (mp), ^{1}H NMR data and/or IR data are shown below.

Example 80

N-(2-aminophenyl)-4-[N'-(3-aminophenyl)ureidomethyl]benzamide (Table 1: Compound 24)

[0154]

mp: 206-208 °C(dec.)

^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 4.35(2H, d, J=5.9 Hz), 4.93(4H, br.s), 6.13(1H, d, J=7.3 Hz), 6.51-6.62(3H, m), 6.74-6.98(3H, m), 7.12-7.18(1H, m), 7.41(2H,d, J=8.1 Hz), 7.94(2H, d, J=8.1 Hz), 8.28(1H, s), 9.61(1H, s)

IR(KBr)cm^{-1}:3356, 3269, 1640, 1555, 1495, 1458, 1308, 1236, 753

Example 81

N-(2-aminophenyl)-4-[N'-(pyridin-3-yl)ureidomethyl]benzamide (Table 1: Compound 87)

[0155]

mp: 187-190 °C

^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 4.39(2H, d, J=5.9 Hz), 4.89(2H, br.s), 6.59(1H, d, J=7.3, 7.3 Hz), 6.77(1H, d, J=6.6 Hz), 6.88(1H, t, J=5.9 Hz), 6.97(1H, ddd, J=1.5, 6.6, 7.3 Hz), 7.16(1H, d, J=8.1 Hz), 7.26(1H, dd, J=4.4, 8.1 Hz), 7.42(2H, d, J=8.8 Hz), 7.95(2H, d, J=8.1 Hz), 7.89-7.96(1H, m), 8.12(1H, dd, J=1.5, 4.4 Hz), 8.56(1H, d, J=3.0 Hz), 8.85(1H, s), 9.62(1H, s)

IR(KBr)cm^{-1}: 3248, 1663, 1541, 1423, 1280, 1054

Example 82

N-(2-aminophenyl)-4-[N'-(3-aminophenyl)thioureidomethyl]benzamide (Table 1: Compound 25)

[0156]

mp: 123 °C(dec.)
^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 4.80(2H, d, J=5.1 Hz), 4.87(2H, s), 5.12(2H, s), 6.36(1H, dd, J=1.5, 8.1 Hz). 6.48-6.63(3H, m), 6.78(1H, d, J=6.6 Hz), 6.94-7.00(2H, m), 7.17(1H, d, J=8.1 Hz), 7.42(2H, d, J=8.1 Hz), 7.92-8.01 (3H, m), 9.46(1H, s), 9.61(1H, s)
IR(KBr)cm^{-1}: 3335, 1616, 1528, 1503, 1456, 1311, 864, 751

Example 83

N-(2-aminophenyl)-4-[N'-(3-nitrophenyl)thioureidomethyl]benzamide (Table 1: Compound 20)

[0157]

mp: 160 °C(dec.)
^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 4.87(2H, d, J=5.1 Hz), 7.27-7.33(3H, m), 7.46-7.63(5H, m), 7.89-7.95(2H, m), 8.05(2H, d, J=8.1Hz), 8.70(1H, s), 8.84(1H, t, J=8.9 Hz), 10.37(1H, s)

Example 84

N-(2-amino-5-fluorophenyl)-4-[N'-(pyridin-3-yl)methylureidomethyl]benzamide (Table 1: Compound 110)

[0158]

mp: (amorphous)
^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 4.77(4H, d, J=5.1 Hz), 4.85(2H, s), 6.81(2H, m), 7.16(1H, dd, J=2.9, 10.3 Hz), 7.39(1H, dd, J=5.1, 8.1 Hz), 7.53(2H, d, J=8.1 Hz), 7.81(1H, d, J=8.1 Hz), 7.93(2H, d, J=8.1 Hz), 8.51(1H, dd, J=1.5, 5.1 Hz), 8.62(1H, d, J =1.5 Hz), 9.66(1H, s)
IR(KBr)cm^{-1}: 3399, 1730, 1638, 1508, 1444, 1411

Example 85

Preparation of N-(2-aminophenyl)-4-[2-[N-(pyridin-3-yl)acetylamino]ethyl]benzamide (Table 1: Compound 77)

[0159]

(85-1) To a suspension of 3.40 g of terephthalaldehydic acid (22.6 mmol) in 25 mL of toluene was added 4 mL of thionyl chloride, and the mixture was heated with stirring at 80 ° C for 2 hours. After cooling and evaporation, the residue was dissolved in 50 mL of THF to give a solution of the acid chloride. To a solution of 4.16 g of the compound from Example 1, the process (1-2) (20.0 mmol) in 10 mL of THF was added 6 mL of triethylamine (42.8 mmol) and then the above solution of the acid chloride was added dropwise under ice-cooling over 30 min.

After stirring for 5 hours, to the mixture was added saturated sodium bicarbonate aq., and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried and evaporated. The residue was purified by column chromatography on silica gel (gradient elution with chloroform to chloroform:ethyl acetate = 10:1) to give 3.42 g of N-[2-(N-tert-butoxycarbonyl)aminophenyl]-4-formylbenzamide (Yield: 50.2 %) as a light brown solid.

^{1}HNMR(270 MHz, $CDCl_3$) δ ppm: 1.52(9H, s), 6.77(1H, br.s), 7.16-7.18(2H, m), 7.23-7.26(1H, m), 7.88(1H, d, J=8.8 Hz), 7.98(2H, d, J=8.8 Hz), 8.13(2H, d, J=8.8 Hz), 9.57(1H, br.s), 10.11(1H, br.s)

IR(KBr)cm^{-1}: 3326, 3251, 1707, 1696, 1659, 1603, 1165

(85-2) A suspension of 3.0 g of the compound from the process (85-1) (8.82 mmol) and 4.5 g of ethoxycarbonylmethyl triphenylphosphine (12.9 mmol) in 10 mL of toluene was stirred in a stream of nitrogen at 80 °C for 5.5 hours. After cooling, the mixture was diluted with ethyl acetate; washed with saturated sodium bicarbonate, water and saturated brine; dried; and evaporated. The residue was purified by column chromatography on silica gel (eluent: chloroform:ethyl acetate = 20:1) to give 3.3 g of ethyl 4-[N-[2-(N-tert-butoxycarbonyl)aminophenyl]amino-

carbonyl]cinnamate (Yield: 91.1 %) as a yellow amorphous solid.

^{1}H NMR(270 MHz, $CDCl_3$) δ ppm: 1.35(3H, t, J=7.3 Hz), 1.52(9H, s), 4.28(2H, q, J=7.3 Hz), 6.52(1H, d, J=15.1 Hz), 6.80(1H, br.s), 7.16-7.25(3H, m), 7.61(2H, d, J=8.1 Hz), 7.71(1H, d, J=15.1 Hz), 7.82(1H, d, 7.3 Hz), 7.98(2H, d, J=8.1 Hz), 9.34 (1H, br.s)

(85-3) To a solution of 2.50 g of the compound from the process (85-2) (6.09 mmol) in 30 mL of THF and 40 mL of methanol was added 10 % Pd/C (wet, 0.5 g) in a stream of nitrogen, and then stirred in a stream of hydrogen for 30 min. After filling with nitrogen, the mixture was filtered to remove the catalyst, and the filtrate was evaporated. To the residue was added diisopropyl ether, and the precipitated solid was collected by filtration and dried to give 2.23. g of N-[2-(N-tert-butoxycarbonyl)aminophenyl]-4-(2-ethoxycarbonylethyl)benzamide (Yield: 88.8 %) as a white solid.

^{1}H NMR(270 MHz, $CDCl_3$) δ ppm: 1.25(3H, t, J=7.3 Hz), 1.52(9H, s), 2.65(2H, t, J=7.3 Hz), 3.02(2H, t, J=7.3 Hz), 4.13(2H, q, J=7.3 Hz), 6.77(1H, br.s), 7.16-7.33(5H, m), 7.78(1H, d, J=8.1 Hz), 7.89(2H, d, J=8.8 Hz), 9.06 (1H, br.s)

(85-4) To a suspension of 2.21 g of the compound from the process (85-3) (5.36 mmol) in 10 mL of methanol and 15 mL of water was added 0.37 g of lithium hydroxide monohydrate (8.82 mmol), and the mixture was stirred at 40 °C for 3 hours. After cooling, to the mixture was added 10 % hydrochloric acid and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried and evaporated. To the residue was added diisopropyl ether, and the precipitated solid was filtered and dried to give 1.87 g of N-[2-(N-tert-butoxycarbonyl)aminophenyl]-4-(2-carboxyethyl)benzamide (Yield: 90.8 %) as awhite solid.

^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 1.45(9H, s), 2.59(2H, t, J=7.3 Hz), 2.91(2H, t, J=7.3 Hz), 7.13-7.20 (2H, m), 7.40(2H, d, J=8.1 Hz), 7.54(2H, dd, J=7.3, 2.1 Hz), 7.88(2H, d, J=8.1 Hz), 8.66(1H, br.s), 9.79(1H, br.s)

(85-5) To a suspension of 0.12 g of the compound from the process (85-4) (0.3 mmol) in 5 mL of benzene were added 0.1 mL of triethylamine (0.7 mmol) and 0.3 g of molecular sieves 4A, and the mixture was stirred in a stream of nitrogen for 0.5 hours. To the mixture was added 0.15 mL of diphenylphosphoryl azide (0.7 mmol), and the mixture was refluxed with heating for 2 hours. After cooling, to the mixture was added 0.4 mL of benzyl alcohol (3.8 mmol), and the mixture was refluxed with heating for additional 2.5 hours. After diluting with ethyl acetate, the reaction mixture was washed with water and saturated brine.

The organic layer was dried and evaporated. The residue was purified by column chromatography on silica gel (eluent: chloroform:ethyl acetate = 4:1) to give 129 mg of N-[2-(N-tert-butoxycarbonyl)aminophenyl]-4-[2-(N-benzyloxycarbonylamino)ethyl]benzamide (Yield: 88 %) as a clear oil.

^{1}H NMR(270 MHz, $CDCl_3$) δ ppm: 1.51(9H, s), 2.89(2H, t, J=7.3 Hz), 3.45-3.54(2H, m), 4.80(1H, m), 5.10 (2H, s), 6.76(1H, br.s), 7.20-7.38(10H, m), 7.79(1H, d, J=8.8 Hz), 7.89(2H, d, J=8.1 Hz), 9.10(1H, br.s)

(85-6) To a solution of 129 mg of the compound from the process (85-5) (0.26 mmol) in 10 mL of methanol was added 10 % Pd/C (wet, 0.05 g) in a stream of nitrogen, and then stirred in a hydrogen stream for 2 hours. After removing the catalyst, the filtrate was evaporated and dried. The residue was dissolved in 5mL of dichloromethane. To the solution were added 0.18 g of 3-pyridineacetic acid hydrochloride (1.04 mmol) and then 0.28 g of triethylamine (2.0 mmol), and the mixture was ice-cooled. Under ice-cooling, to the mixture was added 0.17 g of 2-chloro-1,3-dimethylimidazolinium chloride (1.0 mmol), and the mixture was stirred for 2 hours. To the mixture was added saturated sodium bicarbonate aq., and the mixture was extracted with chloroform. The organic layer was washed with saturated brine, dried and evaporated. The residue was purified by column chromatography on silica gel (eluent: ethyl acetate:methanol = 10:1) to give 50 mg of N-[2-(N-tert-butoxycarbonyl)aminophenyl]-4-[2-[N-(pyridin-3-yl)acetylamino]ethyl]benzamide (Yield: 40 %) as a colorless oil.

^{1}H NMR(270 MHz, $CDCl_3$) δ ppm: 1.48(9H, s), 2.80(2H, t, J=6.6 Hz), 3.42(2H, m), 3.52(2H, s), 6.33(1H, t-like, J=5.9 Hz), 7.09(2H, d, J=8.1 Hz), 7.14-7.20(2H, m), 7.24(1H, dd, J=4.4, 7.3 Hz), 7.41(1H, dd, J=3.7, 5.9 Hz), 7.50(1H, s), 7.58(1H, dd, J=1.5, 5.9 Hz), 7.69(1H, dd, J=3.7, 5.9Hz), 7.75(2H, d, J=8.1 Hz), 8.22(1H, d, J=2.1 Hz), 8.44(1H, dd, J=1.5, 4.4 Hz), 9.49(1H, br.s)

(85-7) To a solution of 50 mg of the compound from the process (85-6) (0.10 mmol) in 2 mL of dioxane and 1 mL of methanol was added 2 mL of 4N hydrochloric acid-dioxane, and the mixture was stirred at room temperature for 2.5 hours. To the mixture was added saturated sodium bicarbonate, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried and evaporated. The residue was dried to give 22 mg of N-(2-aminophenyl)-4-[2-[N-(pyridin-3-yl)acetylamino]ethyl]benzamide (Yield: 59 %) as an amorphous solid.

mp: (amorphous)

^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 2.70-2.90(4H, m), 3.42(2H, s), 4.89 (2H, br.s), 6.60(1H, dd, J=7.3, 7.3Hz), 6.78(1H, d, J=7.3 Hz), 6.97(1H, dd, J=7.3, 7.3 Hz), 7. 16(1H, d, J=7.3 Hz.), 7.29-7.32(3H, m), 7.59(1H, d, J=8.1 Hz), 7.89(1H, d, J=8.1 Hz), 8.22(1H, t-like), 8.41-8.43(2H, m), 9.62(1H, br.s)

Example 86

Preparation of N-(2-aminophenyl)-4-[2-[N-(3-picolyl)aminocarbonyl]ethyl]benzamide (Table 1: Compound 80)

[0160]

(86-1) To a suspension of 0.58 g of the compound from Example 86, the process (86-4) (1.5 mmol) in 5 mL of dichloromethane were added 0.22 g of 3-picolylamine (2.0 mmol) and 0.56 mL of triethylamine (4.0 mmol). Under ice-cooling, to the mixture was added 0.39 g of 2-chloro-1,3-dimethylimidazolinium chloride (2.0 mmol) in 5 mL of dichloromethane, and the mixture was stirred for 1.5 hours. To the mixture was added saturated sodium bicarbonate aq., and the mixture was extracted with chloroform.

The organic layer was washed with water and saturated brine, dried and evaporated. The residue was purified by column chromatography on silica gel (eluent: chloroform:methanol:NH_3 aq. = 100:10:1) to give 0.71 g of N-[2-(N-tert-butoxycarbonyl)aminophenyl]-4-[2-[N-(3-picolyl)aminocarbonyl]ethyl]benzamide (Yield: 94 %) as a light brown oil.

^{1}H NMR(270 MHz, $CDCl_3$) δ ppm: 1.45(9H, s), 2.42(2H, t, J=7.3 Hz), 2.98(2H, t, J=7.3 Hz), 4.32(2H, d, J=6.6 Hz), 6.44(1H, t, J=6.6 Hz), 7.14-7.27(5H, m), 7.48-7.57(3H, m), 7.63-7.68(3H, m), 7.90(1H, d, J=2.1 Hz), 8.43(1H, dd, J=1.4, 4.4 Hz), 9.86(1H, br.s)

(86-2) To a solution of 0.70 g of the compound from the process (86-1) (1.47 mmol) in 5 mL of dioxane was added 5 mL of 4N hydrochloride-dioxane and then 2 mL of methanol, and the mixture was stirred at room temperature for 2 hours. To the mixture was added saturated sodium bicarbonate aq., and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried and evaporated. To the residue was added diisopropyl ether, and the precipitated solid was collected by filtration and dried to give 0.42 g of N-(2-aminophenyl)-4-[2-(N-(3-picolyl)aminocarbonyl]ethyl]benzamide (Yield: 76.3 %) as an opalescent solid.

mp: 168-170 °C

^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 2.47-2.53(2H, m), 2.93(2H, t, J=7.3 Hz), 4.27(2H, d, J=5.9 Hz), 4.90 (2H, br.s), 6.60(1H, dd, J=7.3, 7.3 Hz), 6.78(1H, d, J=8.1 Hz), 6.97(1H, dd, J=6.6, 7.3 Hz), 7.16(1H, d, J=6.6 Hz), 7.28-7.35(1H, m), 7.33(2H, d, J=8.1 Hz), 7.49(1H, dd, J=2.1, 5.9 Hz), 7.89(2H, d, J=8.1 Hz), 8.39-8.44(3H, m), 9.62(1H, br.s)

IR(KBr)cm^{-1}: 3313, 1641, 1523, 1457, 1300, 748, 713

Example 87

Preparation of N-(2-aminophenyl)-4-[(pyridin-3-yl)methylaminocarbonyloxymethyl]benzamide (Table 1: Compound 85)

[0161]

(87-1) To a solution of 1.99 g of methyl 4-hydroxymethylbenzoate (12.0 mmol) in 20 mL of THF were added 1.78 g of N,N'-carbonyldiimidazole (11.0 mmol) at room temperature, and the solution was stirred for an hour. To the solution were added 1.08 g of 3-picolylamine (10.0 mmol) at room temperature, and the mixture was stirred for 3.5 hours and left overnight. Water was added to the solution, and the mixture was extracted with ethyl acetate.

The organic layer was washed with saturated brine, dried and evaporated. The residue was purified by column chromatography on silica gel (eluent: ethyl acetate) to give 2.76 g of N-(4-methoxycarbonyl)benzyloxycarbonyl-3-picolylamine (Yield: 91.9 %) as a white waxy solid.

^{1}H NMR(270 MHz, $CDCl_3$) δ ppm: 3.91(3H, s), 4.40(2H, d, J=5.9 Hz), 5.18(2H, s), 5.50(1H, br.s), 7.24-7.28 (1H, m), 7.40(2H, d, J=8.1 Hz), 7.65(1H, d, J=7.3 Hz), 8.02(2H, d, J=8.8 Hz), 8.50-8.53(2H, m)

(87-2) To a suspension of 2.40 g of the compound from the process (87-1) (8.0 mmol) in 10 mL of methanol and 20 mL of water was added 0.42 g of lithium hydroxide monohydrate (10.0 mmol), and the mixture was stirred at room temperature for 5 hours. To the reaction mixture was added 10 % hydrochloric acid to acidified to pH 2 to 4, and the precipitated solid was collected by filtration and dried to give 1.83 g of N-(4-carboxy)benzyloxycarbonyl-3-picolylamine (79.9 %) as a white solid.

^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 4.24(2H, d, J=5.9 Hz), 5.13(2H, s), 7.33-7.38 (1H, m), 7.46(2H, d, J=8.1 Hz), 7.94(2H, d, J=8.1 Hz), 7.95-8.01(1H, m), 8.46(1H, d, J=5.1 Hz), 8.49(1H, d, J=1.5 Hz), 13.0(1H, br.s)

(87-3) To a suspension of 1.26 g of the compound from the process (87-2) (4.4 mmol) in 20 mL of dichloromethane were slowly added 1.0 mL of oxalyl chloride (11.4 mmol) and then several drops of DMF. The reaction mixture was stirred at room temperature for 10 min. and at 40 °C for additional 30 min. After cooling, the mixture was evaporated and the excess oxalyl chloride was removed by evaporation with toluene. To the residue was added 10 mL of dichloromethane. Under ice-cooling, to the mixture was added dropwise a solution of 0.83 g of the compound from

Example 1, the process (1-2) (4.0 mmol) in 8 mL of dichloromethane and 8 mL of pyridine, and the solution was warmed to room temperature with stirring for 7 hours and left overnight.

To the mixture was added saturated sodium bicarbonate, and the mixture was extracted with chloroform. The organic layer was washed with saturated brine, dried and evaporated. Toluene was added to the residue to azeotropically remove the excess pyridine. The residue was purified by column chromatography on silica gel (eluent: ethyl acetate) to give 1.40 g of N-[2-(N-tert-butoxycarbonyl)aminophenyl]-4-[(pyridin-3-yl)methylaminocarbonyloxymethyl]benzamide (Yield: 73.4 %) as a light brown solid.

^{1}H NMR(270 MHz, $CDCl_3$) δ ppm: 1.51(9H, s), 4.40(2H, d, J=5.9 Hz), 5.19(2H, s), 5.56(1H, m), 7.07(1H, br. s), 7.14-7.31(4H, m), 7.43(2H, d, J=8.1 Hz), 7.65(1H, d, J=8.1 Hz), 7.76(1H, d, J=7.3 Hz), 7.95(2H, d, J=8.1 Hz), 8.52(2H, d, J=4.1 Hz), 9.32(1H,br.s)

(87-4) To a solution of 1.00 g of the compound from the process (87-3) (2.10 mmol) in 10 mL of dioxane and 2 mL of methanol was added 9 mL of 4N hydrochloric acid-dioxane at room temperature, and the mixture was stirred for 2 hours. To the mixture was added saturated sodium bicarbonate and the mixture was extracted with ethyl acetate-methyl ethyl ketone (1:1). The organic layer was washed with saturated brine, dried and evaporated. To the residue was added methanol-diisopropyl ether, and the precipitated solid was collected by filtration and dried to give 0.79 g of N-(2-aminophenyl)-4-[(pyridin-3-yl)methylaminocarbonyloxymethyl]benzamide (Yield: quantitative) as a white solid.

mp: 139-141 °C

^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 4.25(2H, d, J=5.9 Hz), 4.90(2H, s), 5.13(2H, s), 6.60(1H, dd, J=6.6, 7.3 Hz), 6.78(1H, d, J=7.3 Hz), 6.97(1H, dd, J=6.6, 7.3 Hz), 7.17(1H, d, J=7.3 Hz), 7.36(1H, dd, J=4.4, 8.1 Hz), 7.47(2H, d., J=8.1 Hz), 7.67(1H, d, J=8.1 Hz), 7.97(2H, d, J=7.3 Hz), 7.90-8.00(1H, m), 8.46(1H, dd, J=1.5, 5.1 Hz), 8.49(1H, d, J=2.1 Hz), 9.65(1H, br.s)

IR(KBr)cm^{-1}: 3326(br.), 1694, 1637, 1526, 1458, 1147, 750, 712

Example 88

Preparation of N-(2-aminophenyl)-4-[3-(imidazol-1-yl)propylaminocarbonyloxymethyl]benzamide (Table 1: Compound 206)

[0162] The title compound was prepared as described in Example 87.

mp: (amorphous)

^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 1.80-1.89(2H, m), 2.94-3.02(2H, m), 3.98(2H, t, J=7.3 Hz), 4.88(2H, s), 5.11 (2H, s), 6.55-6.63(1H, m), 6.76-6.97(3H, m), 7.10-7.18(2H, m), 7.43-7.48(3H, m), 7.61(1H, s), 7.98(2H, d, J=8.1 Hz), 9.66(1H, s)

Example 89

Preparation of N-(2-aminophenyl)-4-(phenylacetylamino)benzamide (Table 1: Compound 2)

[0163]

(89-1) To a solution of 16.6 g of the compound from Example 1, the process (1-2) (80 mmol) in 120 mL of dichloromethane was added 16.8 mL of triethylamine (120 mmol) and then, was slowly added a solution of 16.0 g of 4-nitrobenzoyl chloride (86.4 mmol) in 40 mL of dichloromethane, and the solution was stirred for 7 hours. To the solution was added saturated sodium bicarbonate aq., and the mixture was extracted with chloroform.

The organic layer was washed with 1N hydrochloric acid, saturated sodium bicarbonate and saturated brine; dried; and evaporated. The residue was washed with diisopropyl ether to give 28.0 g of N-[2-(N-tert-butoxycarbonylamino)phenyl]-4-nitrobenzamide (Yield: 98 %) as a light yellow solid.

^{1}H NMR(270 MHz, $CDCl_3$) δ ppm: 1.53(9H, s), 7.17-7.29(4H, m), 7.85(1H, br.d, J=7.3 Hz). 8.17(2H, d, J=8.8 Hz), 8.32(2H, d, J=8.8 Hz), 9.88(1H, br.s)

(89-2) To a solution of 24.0 g of the compound from the process (89-1) (67.2 mmol) in 80 mL of THF and 80 mL of methanol was added 2.4 g of 10 % Pd/C (wet) in a stream of nitrogen, and the mixture was stirred in a stream of hydrogen for 1.5 hours. After cease of absorption of hydrogen, the catalyst was removed by filtration and the filtrate was evaporated. To the residue were added diisopropyl ether and ethyl acetate, and the precipitated solid was collected by filtration and dried to give 18.96 g of N-[2-(N-tert-butoxycarbonylamino)phenyl]-4-aminobenzamide (Yield: 86 %) as a white solid.

^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 1.46(9H, s), 5.84(2H, s), 6.61(2H, d, J=8.8 Hz), 7.10-7.18(2H, m),

7.46-7.55(2H, m), 7.68(2H, d, J=8.8 Hz), 8.67(1H, s), 9.49(1H, s)

(89-3) To a solution of 1.6 g of the compound from the process (89-2) (4.88 mmol) in 15 mL of dichloromethane were added 0.8 mL of pyridine (9.9 mmol) and 0.96 mL of phenylacetyl chloride (7.26 mmol), and the solution was stirred for one day. After completion of the reaction, water was added and the precipitated crystals were collected by filtration to give 1.66 g of N-[2-(N-tert-butoxycarbonylamino)phenyl]-4-(phenylacetylamino)benzamide (Yield: 76 %).

(89-4) To a solution of 1 g of the compound from the process (89-3) (2.24 mmol) in 25 mL of acetonitrile was added 0.88 mL of iodotrimethylsilane (6.18 mmol) at room temperature, and the solution was stirred for 3 hours. After completion of the reaction, the solution was concentrated. The residue was recrystallized from methanol to give 0.29 g of N-(2-aminophenyl)-4-(phenylacetylamino)benzamide (Yield: 38 %) as white crystals.

mp: 232-237 °C

^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 3.69(2H, s), 4.90(2H, s), 6.60(1H, t, J=7.3 Hz), 6.77(1H, d, J=7.3 Hz), 6.96(1H, t, J=7.3 Hz), 7.15(1H, d, J=7.4 Hz), 7.22-7.35(5H, m), 7.72(2H, d, J=8.8 Hz), 7.95(2H, d, J=8.8 Hz), 9.57 (1H, s), 10.43(1H, s)

IR(KBr)cm^{-1}: 2937, 2764, 1660, 1598, 1506, 1459

[0164] As described in Example 89, the compounds of Examples 90 to 116 were prepared, each of whose melting point (mp), ^{1}H NMR data and/or IR data are shown below.

Example 90

N-(2-aminophenyl)-4-[(4-phenylbutanoyl)amino]benzamide (Table 1: Compound 4)

[0165]

mp: (amorphous)

^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 1.91(2H, hep, J=7.3 Hz), 2.37(2H, t, J=7.3 Hz), 2.64(2H, t, J=7.3 Hz), 5.0 (2H, br.s), 6.61(1H, t, 7.0 Hz), 6.79(1H, dd, J=1.5, 8.1Hz), 6.97(1H, t, J=7.0Hz), 7.10-7.40(6H, m), 7.71(2H, d, J=8.8 Hz), 7.94(2H, d, J=8.8 Hz), 9.57(1H, s), 10.15(1H, s)

IR(KBr)cm^{-1}; 3344, 1687, 1603, 1542, 1460, 1315, 1033, 842, 737

Example 91

N-(2-aminophenyl)-4-[(4-chlorophenylacetyl)amino]benzamide (Table 1: Compound 15)

[0166]

mp: (amorphous)

^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 3.72(2H, s), 7.29-7.43(8H, m), 7.77(2H, d, J=8.8 Hz), 8.00(2H, d, J=8.8 Hz), 10.29(1H, s), 10.52(1H, s)

IR(KBr)cm^{-1}: 3300, 2868, 1664, 1638, 1520

Example 92

N-(2-aminophenyl)-4-[(2-nitrophenylacetyl)amino]benzamide hydrochloride (Table 1: hydrochloride of Compound 19)

[0167]

mp: (amorphous)

^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 4.20(2H, s), 7.20-7.30(3H, m), 7.40-7.45(1H, m), 7.60(2H, d), 7.71-7.77(3H, m), 8.02-8.10(4H, m), 10.27(1H, br.s), 10.64(1H,br.s)

IR(KBr)cm^{-1}: 3263, 1676, 1647, 1518, 1184, 759

Example 93

N-(2-aminophenyl)-4-[(4-nitrophenylacetyl)amino]benzamide (Table 1: Compound 21)

[0168]

mp: 222-226 °C
^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 3.90(2H, s), 4.96(2H, br.s), 6.60(1H, dt, J=1.5, 6.6 Hz), 6.78(1H, dd, J=1.5, 6.6 Hz), 6.97(1H, dt, J=1.5, 6.6Hz), 7.15(1H, dd, J=1.5, 6.6 Hz), 7.63(2H, d, J=8.8 Hz), 7.71(2H, d, J=8.8 Hz), 7.95 (2H, d, J=8.8 Hz), 8.22(2H, d, J=8.8 Hz), 9.59(1H, s), 10.54(1H, s).
IR(KBr)cm^{-1}: 3395, 3334, 1671, 1630, 1519, 1346

Example 94

N-(2-aminophenyl)-4-[(2-aminophenylacetyl)amino]benzamide (Table 1: Compound 22)

[0169]

mp: 177-182 °C(dec.)
^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 3.54(2H, s), 4.88(2H, br.s), 5.09(2H, br.s), 6.55(1H, dd, J=6.6, 7.3 Hz), 6.59 (1H, dd, J=7.3, 7.3 Hz), 6.68(1H, d, J=7.3 Hz), 6.78(1H, d, J=7.3 Hz), 6.96(2H, dd, J=7.3, 7.3 Hz), 7.06(1H, d, J=6.6 Hz), 7.15(1H, d, J=7.3 Hz), 7.71(2H, d, J=8.8 Hz), 7.95(2H, d, J=8.8 Hz), 9.57(1H, br.s), 10.39(1H, br.s)
IR(KBr)cm^{-1}: 3374, 3256(br.), 1683, 1597, 1503, 1317, 1262, 1180, 1153, 747

Example 95

N-(2-aminophenyl)-4-[(4-aminophenylacetyl)amino]benzamide (Table 1: Compound 26)

[0170]

mp: 219-226 °C(dec.)
^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 3.46(2H, s), 4.93(4H, br.s), 6.52(2H, d, J=8.1 Hz), 6.59(1H, dt, J=1.5, 7.3 Hz), 6.77(1H, dd, J=1.4, 7.3 Hz), 6.97(1H, dt, J=1.4, 7.3 Hz), 6.99(2H, d, J=8.1 Hz), 7.15(1H, dd, J=1.5, 7.3 Hz), 7.70(2H, d, J=8.8 Hz), 7.93(2H, d, J=8.8 Hz)
IR(KBr)cm^{-1}: 3278, 3032, 1675, 1628, 1516

Example 96

N-(2-aminophenyl)-4-[(4-methoxyphenylacetyl)amino]benzamide (Table 1: Compound 32)

[0171]

mp: (amouphous)
^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 3.62(2H, s), 3.74(3H, s), 6.90(2H, d, J=8.8 Hz), 7.26(2H, d, J=8.8 Hz), 7.30 (3H, m), 7.39(1H, m), 7.77(2H, d, J=8.8 Hz), 7.99(2H, d, J=8.8 Hz), 10.26(1H, s), 10.44(1H, s)
IR(KBr)cm^{-1}: 3300, 2759, 1670, 1638, 1514, 1250

Example 97

N-(2-aminophenyl)-4-[[4-(N,N-dimethylamino)phenylacetyl]amino]benzamide (Table 1: Compound 53)

[0172]

mp: 140 °C
^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 3.04(6H, s), 3.67(2H, s), 7.16(2H, d, J=8.0 Hz), 7.29-7.40(6H, m), 7.76(2H, d, J=8.8 Hz), 7.99(2H, d, J=8.8 Hz), 10.29(1H, s), 10.47(1H, s)
IR(KBr)cm^{-1}: 3244, 2951, 2639, 1647, 1599, 1507

Example 98

N-(2-aminophenyl)-4-[(4-trifluoromethylphenylacetyl)amino]benzamide (Table 1: Compound 43)

[0173]

mp: (amorphous)
^{1}H NMR(270 MHz, DMSO-d6) δ ppm: 3.84(2H, s), 6.89(1H, t, J=7.4 Hz), 7.00(1H, d, J=7.4 Hz), 7.11(1H, t, J=7.4 Hz), 7.25(1H, d, J=7.4 Hz), 7.57(2H, d, J=8.8 Hz), 7.71(2H, d, J=8.8 Hz), 7.73(2H, d, J=8.8 Hz), 7.97(2H, d, J=8.8 Hz), 9.87(1H, s), 10.54(1H, s)
IR(KBr)cm^{-1}: 3260, 1664, 1605, 1521, 1327, 1119

Example 99

N-(2-aminophenyl)-4-[(pyridin-2-yl)acetylamino]benzamide dihydrochloride(Table 1: hydrochloride of Compound 165)

[0174]

mp: (amorphous)
^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 4.60(2H, s), 7.30-7.46(3H, m), 7.56(1H, d, J=7.4 Hz), 7.79(2H, d, J=8.8 Hz), 7.95(1H, t, J=6.6 Hz), 8.01(1H, d, J=7.4 Hz), 8.11(2H, d, J=8.8 Hz), 8.49(1H, t, J=7.4 Hz), 8.87(1H, d, J=5.1 Hz), 10.46(1H, s)

Example 100

N-(2-aminophenyl)-4-[(pyridin-3-yl)acetylamino]benzamide dihydrochloride(Table 1: hydrochloride of Compound 68)

[0175]

mp: 182-189 °C(dec.)
^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 4.12(2H, s), 7.29-7.59(4H, m), 7.80(2H, d, J=8.8 Hz), 8.05(1H, m), 8.11(2H, d, J=8.8 Hz), 8.57(1H, d, J=8.1 Hz), 8.85(1H, d, J=5.2 Hz), 8.95(1H, s), 10.25(1H, s), 10.48(1H, s)

Example 101

N-(2-aminophenyl)-4-[[3-(pyridin-3-yl)propanoyl]amino]benzamide (Table 1: Compound 69)

[0176]

mp: 184-186 °C
^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 2.80(2H, t, J=7.3 Hz), 3.08(2H, t, J=7.3 Hz), 6.87(1H, t, J=8.0 Hz), 6.99(1H, dd, J=1.4, 8.0 Hz), 7.11(1H, dt, J=1.4, 8.0 Hz), 7.25(1H, d, J=8.0 Hz), 7.70(2H, d, J=8.8 Hz), 7.77(1H, dd, J=5.8, 8.0 Hz), 7.96(2H, d, J=8.8 Hz), 8.22(1H, d, J=8.0 Hz), 8.75(1H, d, J=1.4 Hz), 9.83(1H, s), 10.25(1H, s)

Example 102

N-(2-aminophenyl)-2-chloro-4-[3-(pyridin-3-yl)propanoylamino]benzamide (Table 1: Compound 115)

[0177]

mp: (amorphous)
^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 2.70(2H, t, J=8.1 Hz), 2.96(2H, t, J=7.3 Hz), 4.74(2H, br.s), 6.60(1H, t, J=6.6 Hz), 6.78(1H, d, J=6.6 Hz), 6.95(1H, t, J=6.6 Hz) , 7.19(1H, dd, J=1.5, 7.3 Hz), 7.29(1H, dd, J=5.1, 7.3 Hz), 7.66 (2H, d, J=8.8 Hz), 7.92(2H, d, J=8.8 Hz), 8.48(1H, d, J=2.2 Hz), 9.37(1H, s), 10.00(1H, s)
IR(KBr)cm^{-1}: 3273, 1675, 1519, 1315, 1181, 852, 747

Example 103

N-(2-aminophenyl)-4-[[N-(pyridin-3-yl)methyl-N-trifluoroacetylamino]acetylamino]benzamide (Table 1: Compound 106)

[0178]

mp: 145 °C(dec.)
^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 4.18 and 4.42(total 2H, s), 4.73 and 4.83(total 2H, s), 4.87(2H, br.s), 6.60 (1H, dd, J=7.3, 8.1 Hz), 6.78(1H, d, J=8.1 Hz), 6.96(1H, dd, J=7.3, 7.3 Hz), 7.16(1H, d, J=8.1 Hz), 7.35-7.45(1H, m), 7.66(2H, d, J=5.9 Hz), 7.70-7.80(1H, m), 7.90-8.00(2H, m), 8.51-8.55(1H, m), 8.58(1H, s), 9.60(1H, br.s), 10.36 and 10.43(total 1H, br.s)

Example 104

N-(2-aminophenyl)-4-[[N-(pyridin-3- yl)methylamino]acetylamino]benzamide (Table 1: Compound 104)

[0179]

mp: 160 °C(dec.)
^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 3.30(2H, s), 3.79(2H, s), 4.88(2H, s), 6.60(1H, dd, J=7.3, 7.3 Hz), 6.78(1H, d, J=8.1 Hz), 6.97(1H, dd, J=7.3, 8.1 Hz), 7.16(1H, d, J=8.1 Hz), 7.74(2H, d, J=8.8 Hz), 7.80(1H, d, J=7.3 Hz), 7.95(2H, d, J=8.1 Hz), 8.46(1H, d, J=3.7 Hz), 8.57(1H, s), 9.57(1H, s), 10.08(1H, br.s)
IR(KBr)cm^{-1}: 3298, 1693, 1637, 1602, 1544, 1454, 1262, 848, 762

Example 105

N-(2-aminophenyl)-4-[N-(pyridin-3-yl)methyloxamoylamino]benzamide (Table 1: Compound 103)

[0180]

mp: (amorphous)
^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 4.43(2H, d, J=6.6 Hz) 4.90(2H, br.s), 6.60(1H, dd, J=6.6, 7.3Hz), 6.78(1H, d, J=7.3 Hz), 6.97(1H, ddd, J=1.5, 6.6, 7.3 Hz), 7.16(1H, d, J=7.3 Hz), 7.37(1H, dd, J=4.4, 8.1 Hz), 7.73(1H, d, J=8.1 Hz), 7.96 and 7.96(4H, AA'BB', J=9.4 Hz), 8.47(1H, dd, J=1.5, 5.1 Hz), 8.56(1H, d, J=1.5 Hz), 9.59 (1H, s), 9.67(1H, t, J=6.6 Hz), 10.92(1H, br.s)
IR(KBr)cm^{-1}: 3299, 1644, 1518, 1320, 1119, 748

Example 106

N-(2-aminophenyl)-4-[[N-(pyridin-3-yl)methyl-N-nicotinoylamino]acetylamino]benzamide (Table 1: Compound 105)

[0181]

mp: (amorphous)
^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 4.11(major 2H, s), 4.26(minor 2H, s), 4.75(major 2H, s), 4.65(minor 2H, s), 4:88(total 2H, br.s), 6.60(total 1H, dd, J=7.3, 8.1 Hz), 6.78(total 1H, d, J=7.3 Hz), 6.97(total 1H, dd, J=7.3, 8.1 Hz), 7.15(total 1H, d, J=8.1 Hz), 7.41-7.95(total 8H, m), 8.46-8.52(total 1H, m) , 8.63-8.70(total 2H, m) , 9.59(total 1H, s), 10.22(major 1H, br.s), 10.37(minor 1H, br.s)
IR(KBr)cm^{-1}: 3269, 1701, 1637, 1603, 1534, 1506, 1312, 1254, 752

Example 107

N-(2-aminophenyl)-4-[[4-(pyridin-3-yl)butanoyl]amino]benzamide (Table 1: Compound 70)

[0182]

mp: 165-167 °C(dec.)

^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 1.88-1.99(2H, m), 2.68(2H, t, J=7.3 Hz), 2.39(2H, t, J=7.3 Hz), 6.78-6.81 (1H, m), 6.94-6.99(1H, m), 7.15-7.18(1H, m), 7.34-7.39(1H, m), 7.69-7.72(3H, m), 7.94(2H, d, J=8.8 Hz), 8.43-8.48 (2H, m)
IR(KBr)cm^{-1}: 3291, 1660, 1626, 1308, 1261, 1182, 1027, 825, 747

Example 108

N-(2-aminophenyl)-4-[[N-(pyridin-3-yl)methyl-N-methylamino]acetylamino]benzamide (Table 1: Compound 107)

[0183]

mp: 154-155 °C
^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 2.28(3H, s), 3.27(2H, s), 3.71(2H, s), 4.88(2H, br.s), 6.60(1H, dd, J=6.6, 7.3Hz), 6.78(1H, d, J=8.1Hz), 6.97(1H, dd, J=7.3, 8.1 Hz), 7.16(1H, d, J=8.1 Hz), 7.38(1H, dd, J=2.9, 8.1 Hz), 7.77 (2H, d, J=8.8 Hz), 7.75-7.85(1H, m), 7.95(2H, d, J=8.8 Hz), 8.47(1H, d, J=1.5 Hz), 8.49(1H, s), 9.56(1H, s), 10.62 (1H, br.s)

Example 109

N-(2-aminophenyl)-4-[N-(pyridin-3-yl)oxyacetylamino]benzamide (Table 1: Compound 65)

[0184]

mp: 175-179 °C
^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 4.86(2H, s), 4.90(2H, br.s), 6.60(1H, d, J=7.3, 7.3 Hz), 6.78(1H, d, J=7.3 Hz), 6.97(1H, dd, J=6.6, 7.3 Hz), 7.16(1H, d, J=8.1 Hz), 7.34-7.47(2H, m), 7.76(2H, d, J=8.8 Hz), 7.98(2H, d, J=8.8 Hz), 8.22(1H, d, J=3.6 Hz), 8.39(1H, d, J=2.9 Hz), 9.60(1H, br.s), 10.40(1H, br.s)
IR(KBr)cm^{-1}: 3321, 1655, 1530, 1276, 1231, 1068, 757

Example 110

N-(2-aminophenyl)-4-[4-(pyridin-3-yl)-1,4-dioxobutylamino]benzamide (Table 1: Compound 98)

[0185]

mp: 190-194 °C
^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 2.08(2H, t, J=6.4 Hz), 3.41(2H, t, J=6.4 Hz), 4.86(2H, s), 6.59(1H, t, J=5.6 Hz), 6.78(1H, d, J=7.9 Hz), 6.96(1H, t, J=7.4 Hz), 7.15(1H, d, J=7 Hz), 7.58(1H, dd, J=4.9, 7.9Hz), 7.70(2H, d, J=8.9 Hz), 7.94(2H, d, J =8.9 Hz), 8.35(1H, d, J=7.9 Hz), 8.81(1H, d, J=4 Hz), 9.18(1H, s), 9.56(1H, s), 10.32(1H, s)
IR(KBr)cm^{-1}: 3317, 1691, 1652, 1601, 1522, 1312, 982, 847, 764, 701

Example 111

N-(2-aminophenyl)-4-[3-[N-(pyridin-3-yl)amino]-1,3-dioxopropylamino]benzamide (Table 1: Compound 93)

[0186]

mp: 196 °C(dec.)
^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 3.57(2H, s), 4.87(2H, s), 6.57-6.62(1H, m), 6.76-6.79(1H, m), 6.94-6.99(1H, m), 7.14-7.17(1H, m), 7.33-7.38(1H, m), 7.73(2H, d, J=8.8 Hz), 7.97(2H, d, J=8.8 Hz), 8.05-8.08(1H, m), 8.27-8.30 (1H, m), 8.75-8.76(1H, m), 9.59(1H, s), 10.44(1H, s), 10.47(1H, s)
IR(KBr)cm^{-1}: 3410, 3315, 1685, 1655, 1625, 1536, 1428, 1362, 1263, 1201, 744

Example 112

N-(2-aminophenyl)-4-[N-(pyridin-3-yl)methoxyacetylamino]-3-methylbenzamide (Table 1: Compound 101)

[0187]

mp: 178-181 °C(dec.)
^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 2.28(3H, s), 4.22(2H, s), 4.71(2H, s), 4.89(2H, br.s), 6.60(1H, dd, J=7.3, 7.3 Hz), 6.78(1H, d, J=8.1 Hz), 6.97(1H, dd, J=7.3, 8.1 Hz), 7.16(1H, d, J=7.3 Hz), 7.43(1H, dd, J=4.4, 8.1 Hz), 7.71 (1H, d, J=8.1 Hz), 7.79-7.89(3H, m), 8.54(1H, dd, J=1.5, 4.4 Hz), 8.66(1H, d, J=1.5Hz), 9.36(1H, br.s), 9.60(1H, br.s)
IR(KBr)cm^{-1}: 3394, 3269, 1683, 1630, 1593, 1521, 1460, 1131, 750, 716

Example 113

N-(2-aminophenyl)-4-[N-(thiophen-3-yl)methoxyacetylamino]benzamide (Table 1: Compound 195)

[0188]

mp: 186-189 °C
^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 4.11(2H, s), 4.63(2H, s), 4.89(2H, br.s), 6.60(1H, dd, J=7.3, 7.3Hz), 6.78 (1H, d, J=8.1 Hz), 6.97(1H, dd, J=7.3, 7.3 Hz), 7.12-7.19(2H, m), 7.53-7.57(2H, m), 7.78(2H, d, J=8.8 Hz), 7.95 (2H, d, J=8.8 Hz), 9.58(1H, br.s), 10.04(1H, br.s)
IR(KBr)cm^{-1}: 3341, 3248, 1694, 1631, 1611, 1506, 1314, 1126

Example 114

N-(2-aminophenyl)-4-[N-methyl-N-(Pyridin-3-yl)methoxyacetylamino]benzamide (Table 1: Compound 102)

[0189]

mp: 180-183 °C(dec.)
^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 3.24(3H, s), 4.08(2H, br.s), 4.50(2H, s), 4.94(2H, br.s), 6.60(1H, dd, J=7.3, 7.3 Hz), 6.79(1H, d, J=8.1 Hz), 6.98(1H, dd, J=7.3, 8.1 Hz), 8.03(1H, d, J=8.1 Hz), 8.48-8.50(2H, m), 9.72(1H, br.s)
IR(KBr)cm^{-1}: 3395, 3283, 1683, 1639, 1604, 1506, 1459, 1307, 1124

Example 115

N-(2-aminophenyl)-4-[N-(pyridin-2- yl)methoxyacetylamino]benzamide (Table 1: Compound 167)

[0190]

mp: 171-173 °C
^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 4.26(2H, s), 4.74(2H, s), 4.89(2H, br.s), 6.60(1H, dd, J=6.6, 8.1 Hz), 6.78 (1H, d, J=7.3Hz), 6.97(1H, ddd,J=1.5, 7.3, 8.1 Hz), 7.16(1H, d, J=7.3 Hz), 7.35(1H, dd, J=5.1, 6.6 Hz), 7.80(2H, d, J=8.1 Hz), 7.80-7.89(1H, m), 7.97(2H, d, J=8.1 Hz), 8.59(1H, d, J=4.4 Hz), 9.59(1H, br.s), 10.30(1H, br.s)
IR(KBr)cm^{-1}: 3391, 3258, 1678, 1629, 1593, 1517, 1128, 767, 742

Example 116

N-(2-aminophenyl)-4-[N-(N-nicotinoylamino)acetylamino]benzamide (Table 1: Compound 96)

[0191]

mp: 218-220 °C(dec.)
^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 4.13(2H, d, J=5.9 Hz), 4.89(2H, s), 6.59(1H, dd, J=7.3, 7.3 Hz), 6.77(1H, d, J=8.1 Hz), 6.96(1H, dd, J=7.3, 8.1 Hz), 7.15(1H, d, J=7.3Hz), 7.55(1H, dd, J=5.1, 8.1Hz), 7.73(2H, d, J=8.8 Hz), 7.96(2H, d, J=8.8 Hz), 8.25(1H, d, J=8.1 Hz), 8.74(1H, d, J=5.1 Hz), 9.07(1H, d, J=1.5 Hz), 9.13(1H, t-like, J=5.9 Hz), 9.58(1H, s), 10.36(1H, s)

Example 117

Preparation of N-(2-aminophenyl)-4-[(pyridin-3-yl)methoxyacetylamino]benzamide (Table 1: Compound 100)

[0192]

(117-1) To a suspension of 4. 4g of sodium hydride (60 % oil dispersion; 110 mmol) in 300 mL of THF were added dropwise 10.91 g of 3-pyridinemethanol (100 mmol) in 20 mL of THF at room temperature, and the mixture was stirred at room temperature for 2 hours. The resulting white suspension was ice-cooled, and 19.51 g of tert-butyl bromoacetate (100 mmol) in 20 mL of THF was added dropwise, maintaining the inner temperature within 10 to 12 °C. The suspension was warmed to room temperature with stirring for 3 hours, and then left overnight. After adding water and saturated sodium bicarbonate aq., the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried and evaporated. The residue was purified by column chromatography on silica gel (gradient elution with n-hexane:ethyl acetate = 1:1 to ethyl acetate) to give 7.56 g of tert-butyl (pyridin-3-yl)methoxyacetate (33.8 %) as a light brown oil.

^{1}H NMR(270 MHz, $COCl_3$) δ ppm: 1.49(9H, s), 4.03(2H, s), 4.64(2H, s), 7.30(1H, dd, J=4.9, 7.3 Hz), 7.76 (1H, d, J=7.3 Hz), 8.56(1H, d, J=4.9 Hz), 8.60(1H, s)

(117-2) Under ice-cooling, 12 mL of trifluoroacetic acid was added to 3.5 g of the compound from the process (117-1) (15.7 mmol), and the solution was stirred at room temperature for 6 hours. Part of trifluoroacetic acid was removed by evaporation to give a mixture of (pyridin-3-yl)methoxyacetic acid and trifluoroacetic acid (6.5 g). The mixture was dissolved in 70 mL of dichloromethane. To the solution was added 25 mL of pyridine and then, was slowly added dropwise under ice-cooling, 2.37 g of 2-chloro-1,3-dimethylimidazolinium chloride (14.0 mmol) in 20 mL of dichloromethane over 30 min, and the solution was stirred under ice-cooling for additional 5 hours. To the solution was added saturated sodium bicarbonate aq. , and stirring was continued until foaming ceased. The mixture was extracted with chloroform. The organic layer was washed with saturated brine, dried and evaporated. The residue was purified by column chromatography on silica gel (gradient elution with ethyl acetate to ethyl acetate:methanol = 10:1) to give 4.78 g of N-[2-(N-tert-butoxycarbonyl)aminophenyl]-4-[N-(pyridin-3-yl)methoxyacetylamino]benzamide (Yield: 62 %) as a 1:1 (molar ratio) mixture with DMI (1,3-dimethyl-2-imidazolinone).

^{1}H NMR(270 MHz, $CDCl_3$) δ ppm: 1.51(9H, s), 4.15(2H, s), 4.70(2H, s), 6.92(1H, br.s), 7.15-7.29(3H, m), 7.37(1H, dd, J=7.3, 5.1 Hz), 7.67(2H, d, J=8.8 Hz), 7.71-7.79(2H, m), 7.96(2H, d, J=8.8 Hz), 8.41(1H, s), 8.62-8.66 (2H, m), 9.23(1H, br.s)

(117-3) To a solution of 2.39 g of the compound from the process (117-2) (4.0 mmol) in 28 mL of dichloromethane was added 55 mL of 15 %(vol/vol) trifluoroacetic acid/dichloromethane, and the solution was stirred at room temperature for 7 hours. The solution was neutralized with saturated sodium bicarbonate, and then water was added. The reaction mixture was stirred at room temperature and extracted with a 2:1 mixture of ethyl acetate-methyl ethyl ketone, a 2:1 mixture of ethyl acetate-THF, and ethyl acetate, in sequence. The combined organic layer was washed with saturated brine and dried over anhydrous sodium sulfate. After removing the dehydrating reagent by filtering, the filtrate was concentrated. To the residue thus obtained were added methanol and diisopropyl ether, and the precipitated solid was collected by filtration and dried to give 1.29 g of N-(2-aminophenyl)-4-[N-(pyridin-3-yl)methoxyacetylamino]benzamide (Yield: 85.6 %) as a dark brown solid.

^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 4.19(2H, s), 4.68(2H, s), 4.90(2H, br.s), 6.60(1H, ddd, J=1.5, 7.3, 8.1 Hz), 6.78(1H, dd, J=1.5, 8.1 Hz), 6.97(1H, dd, J=7.3, 7.3 Hz), 7.15(1H, d, J=7.3 Hz), 7.42(1H, dd, J=4.4, 8.1 Hz), 7.77(2H, d, J=8.8 Hz), 7.85(1H, d, J=7.3 Hz), 7.96(2H, d, J=8.8 Hz), 8.54(1H, dd, J=1.5, 5.1 Hz), 8.63(1H, s), 9.58 (1H, s), 10.09(1H, s)

IR(KBr)cm^{-1}: 3403, 3341, 3250, 1694, 1630, 1610, 1506, 1314, 1259, 1118, 764

Example 118

Preparation of N-(2-aminophenyl)-4-(N-benzylamino)carbonylbenzamide (Table 1: Compound 8)

[0193]

(118-1) To a suspension of 13.0 g of monomethyl terephthalate (72.2 mmol) in 100 mL of toluene was added dropwise 10 mL of thionyl chloride at room temperature. After stirring at 80 °C for 3 hours, the solvent and an excess amount of thionyl chloride were removed by evaporation. The residue was suspended in 100 mL of dioxane, and 9.98 g of 2-nitroaniline (72.2 mmol) were added to the suspension, followed by refluxing with heating for 4 hours.

After cooling and evaporation, the residue was washed with methanol to give 20.3 g of N-(2-nitrophenyl)-

4-methoxycarbonylbenzamide (Yield: 93.7 %) as a yellow solid.

^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 3.91(3H, s), 7.43-7.49(1H, m), 7.76-7.78(2H, m), 8.03(1H, d, J=8.1 Hz), 8.08(2H, d, J=8.8 Hz), 8.14(2H, d, J=8.8 Hz), 10.94(1H, s)

(118-2) To a solution of 4.24 g of the compound from the process (118-1) in 50 mL of THF and 50 mL of methanol was added 0.4 g of 10 % Pd/C in a stream of nitrogen, and the mixture was stirred in a stream of hydrogen for 1.5 hours. The catalyst was removed by filtration, and the filtrate was evaporated. The residue was washed with methanol to give 3.4 g of N-(2-aminophenyl)-4-methoxycarbonylbenzamide (Yield: 87.5 %) as a light yellow solid.

^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 3.90(3H, s), 4.95(2H, s), 6.60(1H, dd, J=7.3, 8.1 Hz), 6.78(1H, d, J=7.3Hz), 6.99(1H, dd, J=7.3, 7.3 Hz), 7.17(1H, d, J=7.3 Hz), 8.08(2H, d, J=8.1 Hz), 8.11(2H, d, J=8.1 Hz), 9.85 (1H, s)

(118-3) To a solution of 2.71 g of the compound from the process (118-2) (10.0 mmol) in 100 mL of dioxane and 50 mL of water was added 5 % sodium hydroxide aq. under ice-cooling, and then were added dropwise 2.62 g of di-tert-butyl dicarbonate (12.0 mmol) in 40 mL of dioxane. The mixture was stirred at room temperature for 4 hours and left overnight. To the mixture were added saturated brine and ethyl acetate, and the two layers were separated. The aqueous layer was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried and evaporated. The residue was washed with methanol to give 3.54 g of N-[2-(N-tert-butoxycarbonyl)amino henyl]-4-methoxycarbonylbenzamide (Yield: 95.7 %) as a light brown solid.

^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 1.44(9H, s), 3.90(3H, s), 7.12-7.24(2H, m), 7.55-7.58(2H, m), 8.09(2H, d, J=8.8 Hz), 8.10(2H, d, J=8.8 Hz), 8.72(1H, s), 10.00(1H, s)

(118-4) A suspension of 3.00 g of the compound from the process (118-3) (8.10 mmol) in 50 mL of methanol and 25 mL of 0.5N lithium hydroxide aq. was heated with stirring at 40 °C for 5 hours. After removing methanol by evaporation, to the residue was added 1N hydrochloric acid, and the mixture was extracted with ethyl acetate. The organic layer was washed with a small amount of water and saturated brine, dried and evaporated. The residue was washed with methanol to give 2.24 g of terephthalic mono-2-(N-tert-butoxycarbonyl)aminoanilide (Yield: 77.6 %) as a light brown solid.

^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 1.45(9H, s), 7.12-7.21(2H, m), 7.53-7.58(2H, m), 8.06(2H, d, J=8.8 Hz), 8.10(2H, d, J=8.8 Hz), 8.71(1H, s), 9.97(1H, s)

(118-5) To a suspension of 0.20 g of the compound from the process (118-4) (0.56 mmol) in 4 mL of dichloromethane were added 0.14 g of benzylamine (1.3 mmol) and then 0.21 mL of triethylamine (1.5mmol). To the solution was added 0.25 g of 2-chloro-1,3-dimethylimidazolium chloride (1.48 mmol) under ice-cooling, and then the mixture was stirred under ice-cooling for an hour and at room temperature for an hour. After diluting with chloroform and adding water, the aqueous layer was extracted with chloroform.

The combined organic layer was washed with saturated brine, dried and evaporated. The residue was purified by column chromatography on silica gel (eluent: chloroform:methanol = 10:1). The solid obtained was washed with diethyl ether to give 279 mg of N-(2-tert-butoxycarbonylaminophenyl)-4-(N-benzylamino)carbonylbenzamide (Yield: 62.6 %) as a white solid.

^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 1.45(9H, s), 4.52(2H, d, J=5.8 Hz), 7.13-7.28 (4H, m), 7.34-7.35(3H, m), 7.56(2H, d, J=8.1Hz), 8.05(4H, s), 8.71(1H, br.s), 9.23(1H, t), 9.94(1H, s)

(118-6) To 151 mg of the compound from the process (118-5) (0.339 mmol) was added 5 mL of 4N hydrochloric acid-dioxane at room temperature, and the mixture was stirred for 4 hours. After evaporation, the mixture was partitioned between ethyl acetate and saturated sodium bicarbonate aq. After removing the precipitate, the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with saturated brine, dried and evaporated. To the residue was added diethyl ether, and the precipitate was collected by filtration and dried to give 78 mg of N-(2-aminophenyl)-4-(N-benzylamino)carbonylbenzamide (Yield: 67 %) as a white solid.

mp: 239-241 °C(dec.)

^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 4.51(2H, s), 4.93(2H, br.d), 6.60(1H, dd, J=7.3, 7.3 Hz), 6.78(1H, d, J=8.1 Hz), 6.95(1H, dd, J=7.3, 8.3 Hz), 7.18(1H, d), 7.23-7.35(5H, m), 8.01(2H, d, J=8.8 Hz), 8.07(2H, d, J=8.8 Hz), 9.22(1H, br.t), 9.81(1H, br.s)

[0194] As described in Example 118, the compound of Example 119 was prepared, whose melting point (mp), ^{1}H NMR data and IR data are shown below.

Example 119

N-(2-aminophenyl)-4-[N-(2-phenylethyl)amino]carbonylbenzamide (Table 1: Compound 9)

[0195]

mp: 237-240 °C(dec.)
^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 2.87(2H, t, J=7.3 Hz), 3.51(2H, dt, J=5.9, 7.3Hz), 4.94(2H, br. s), 6.60(1H, dd, J=7.3, 7.3 Hz), 6.78(1H, d, J=7.3 Hz), 6.98(1H, dd, J=7.3, 7.3 Hz), 7.15-7.34(6H, m), 7.93(2H, d, J=8.1 Hz), 8.04(2H, d, J=8.1 Hz), 8.73(1H, t, J=5.1 Hz), 9.76(1H, br.s)
IR(KBr)cm^{-1}: 3396, 3320, 1625, 1602, 1539, 1458, 1313, 699

Example 120

Preparation of N-(2-aminophenyl)-4-[N-(4-nitrophenoxyacetyl)amino]benzamide (Table 1: Compound 54)

[0196]

(120-1) To a solution of 3 g of the compound from Example 89, the process (89-2) (9.2 mmol) and 2.16 g of 4-nitrophenoxyacetic acid (11.0 mmol) in 7 mL of DMF were added 2.82 g of dicyclohexylcarbodiimide (13.8 mmol) in 5 mL of DMF and a catalytic amount of N,N-dimethylaminopyridine, and the mixture was stirred for one day. After completion of the reaction, ethyl acetate was added to the mixture, insolubles were filtered off through celite, and the solvent was removed by evaporation.

The residue was recrystallized from chloroform to give 2.34 g of N-[2-(tert-butoxycarbonylamino)phenyl]-4-[(4-nitrophenoxyacetyl)amino]benzamide (Yield: 50 %).

^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 1.45(9H, s), 4.97(2H, s), 7.12-7.26(3H, m), 7.23(2H, d, J=8.8 Hz), 7.53 (1H, dt, J=2.2, 7.3 Hz), 7.79(2H, d, J=8.8 Hz), 7.95(2H, d, J=8.8 Hz), 8.25(2H, d, J=8.8 Hz), 8.71(1H, s), 9.79(1H, s), 10.52(1H, s)

(120-2) To a solution of 0.7 g of the compound from the process (120-1) (1.38 mmol) in 10 mL of acetonitrile was added 1.26 mL of iodotrimethylsilane (8.85 mmol) at room temperature, and the solution was stirred for 2 hours. After completion of the reaction, the solution was concentrated. Ethyl acetate was added to the residue, the solution was stirred for 20 min, and the precipitated crystals were collected by filtration. The crystals were dissolved in methyl ethyl ketone. The solution was washed with saturated sodium thiosulfate aq. and saturated brine in sequence, dried over anhydrous magnesium sulfate, and evaporated. The residue was washed with ethyl acetate to give 0.22 g of N-(2-aminophenyl)-4-[N-(4-nitrophenoxyacetyl)amino]benzamide (Yield: 39 %) as white crystals.

mp: 212-215 °C(dec.)

^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 4.97(2H, s), 6.88(1H, t, J=7.3 Hz), 6.99(1H, d, J=7.3 Hz), 7.11(1H, t, J=7.3Hz), 7.23(2H, d, J=8.8Hz), 7.24(1H,m), 7.77(2H, d, J=8.8 Hz), 8.00(2H, d, J=8.8 Hz), 8.25(2H, d, J=8.8 Hz), 9.89(1H, s), 10.52(1H, s)

IR(KBr)cm^{-1}: 3382, 3109, 1650, 1591, 1508, 1341

Example 121

Preparation of N-(2-aminophenyl)-4-[(4-aminophenoxyacetyl)amino]benzamide (Table 1: Compound 55)

[0197] To a solution of 1.41g of the compound from Example 120, the process (120-1) (2.78 mmol) in 15 mL of methanol and 25 mL of THF was added 10 % Pd-C, and the mixture was stirred in an atmosphere of hydrogen, at room temperature for an hour. After completion of the reaction, the catalyst was filtered off and the filtrate was concentrated. The residue was triturated with diisopropyl ether to give 1.1 g of N-[2-(tert-butoxycarbonylamino)phenyl]-4-[(4-aminophenoxyacetyl)amino]benzamide.

[0198] The product was dissolved in 15 mL of acetonitrile. To the solution was added 0.74 mL of iodotrimethylsilane (5.20 mmol), and the mixture was stirred at room temperature for 3 hours. After completion of the reaction, the mixture was evaporated. The residue was washed with methyl ethyl ketone to give 0.86 g of N-(2-aminophenyl)-4-[(4-aminophenoxyacetyl)amino]benzamide (Yield: 83 %).

mp: (amorphous)

^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 4.82(2H, s), 7.13(2H, d, J=8.8 Hz), 7.30-7.48 (6H, m), 7.82(2H, d, J=8.8 Hz), 8.03(2H, d, J=8.8 Hz), 10.34(1H, s), 10.46(1H, s)

IR(KBr)cm^{-1}: 2873, 2590, 1680, 1602, 1505, 1243

Example 122

Preparation of N-(2-aminophenyl)-4-[N-(pyridin-3-yl)methoxycarbonylaminomethyl]benzamide 0.5 fumarate (Table 1: fumarate of Compound 82)

[0199] To 10 mL of methanol were added 310 mg of the compound from Example 44, and the mixture was heated to dissolve the solid. To the solution was added 96 mg of fumaric acid in methanol, and the solution was cooled. The precipitated crystals were collected by filtration and recrystallized from 5 mL of methanol to give 200 mg of the desired product (Yield: 56 %).

mp: 166-167 °C

^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 4.28(2H, d, J=6.6 Hz), 5.10(2H, s), 6.60(1H, t, J=8.0 Hz), 6.63(1H, s), 6.78 (1H, d, J=8.0 Hz), 6.90-7.50(5H, m), 7.70-8.00(4H, m), 8.53(1H, d, J=3.6 Hz), 8.60(1H, s), 9.63(1H, s)

IR(KBr)cm^{-1}: 3332, 1715, 1665, 1505, 1283, 1136, 1044, 983, 760, 712

Elementary analysis for $C_{21}H_{20}N_4O_3+1/2C_4H_4O_4$			
	C	H	N
Calculated	63.59	5.10	12.90
Observed	63.56	5.22	12.97

[0200] As described in Example 122, the compounds of Examples 123 to 125 are prepared, each of whose melting point (mp), ^{1}H NMR data, IR data and/or elementary analysis data are shown below.

Example 123

N-(2-aminophenyl)-4-[N-(pyridin-3-yl)methoxycarbonylaminomethyl]benzamide maleate (Table 1: maleate of Compound 82)

[0201]

mp: 123-124 °C

^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 4.28(2H, d, J=6.6 Hz), 5.11(2H, s), 6.24(2H, s), 6.66(1H, t, J=8.0 Hz), 6.83 (1H, d., J=8.0 Hz), 6.90-8.00(9H, m), 8.56(1H, d, J=3.6 Hz), 8.62(1H, s), 9.69(1H, s)

IR(KBr)cm^{-1}: 3298, 1719, 1546, 1365, 1313, 1250, 1194, 1149, 1044, 993, 862, 751

Elementary analysis for $C_{21}H_{20}N_4O_3+C_4H_4O_4+0.3\ H_2$			
	C	H	N
Calculated	60.31	4.98	11.25
Observed	60.52	5.12	11.03

Example 124

N-(2-aminophenyl)-4-[N-(pyridin-3-yl)methoxycarbonylaminomethyl]benzamide hydrochloride (Table 1: hydrochloride of Compound 82)

[0202]

mp: 140(dec.) °C

^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 4.31(2H, d, J=5.8 Hz), 5.24(2H, s), 7.10-7.60(6H, m), 7.90-8.50(5H, m), 8.70-8.90(2H, m), 10.46(1H, s)

IR(KBr)cm^{-1}: 2553, 1715, 1628, 1556, 1486, 1254, 1049, 778, 687

Example 125

N-(2-aminophenyl)-4-[N-(pyridin-3-yl)oxyacetylaminomethyl]benzamide 0.7 fumarate (Table 1: fumarate of Compound 61)

[0203] As described in Example 122, the title compound was prepared from the compound of Example 43.

mp: 154-155 °C
^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 4.42(2H, d, J=5.9 Hz), 4.69(2H, s), 6.60(1H, t, J=8.0 Hz), 6.63(0.7H, s), 6.78 (1H, d, J=8.0 Hz), 6.90-7.50(6H, m), 7.93(2H, d, J=8.0 Hz), 8.20-8.40(2H, m) , 8.82(1H, br.s), 9.63(1H, s)
IR(KBr)cm^{-1}: 3324, 1709, 1631, 1521, 1457, 1428, 1260, 1064, 806, 698

Elementary analysis for $C_{21}H_{20}N_4O_3$+0.7 $C_4H_4O_4$+0.7 H_2O			
	C	H	N
Calculated	60.79	5.19	11.91
Observed	60.95	5.20	11.75

Comparative Example 1

N-(3-aminophenyl)-4-[N-(pyridin-3-yl)methoxycarbonylaminomethyl]benzamide

[0204] As described in Example 44, the title compound was evaluated using ALP activity as an indicator.

Experimental procedure

[0205] To each well of a 96-well plate was placed 0.1 mL of A2780 cells (15,000 cells/well) and the next day was added 0.1 mL of a sequential dilute of test solution with the medium. After incubation for 3 days, the cells on the plate were washed twice with a TBS buffer (20 mM Tris, 137mMNaCl, pH 7.6). Then, to each well was added 0.05 mL of 0.6 mg/mL p-nitrophenylphosphate (9.6 % diethanolamine, 0.5 mM $MgCl_2$ (pH 9.6)) solution, and the plate was incubated at room temperature for 30 min. The reaction was quenched with 0.05 mL/well of 3N sodium hydroxide aq. For each well, an absorbance at 405 nm was measured to determine the minimum concentration of the drug inducing increase of ALP activity (ALPmin).

Results

[0206] The results are shown in Table 5.

Table 5:

Differentiation-inducing action to A2780 cells	
Test Compound	ALPmin (μM)
Example 1	1
Example 2	3
Example 3	3
Example 4	1
Example 5	1
Example 6	1
Example 7	1
Example 8	1
Example 9	1
Example 10	3

Table 5: (continued)

Differentiation-inducing action to A2780 cells	
Test Compound	ALPmin (μM)
Example 11	1
Example 13	1
Example 15	3
Example 16	3
Example 17	3
Example 18	3
Example 23	1
Example 24	1
Example 25	3
Example 26	1
Example 27	10
Example 28	10
Example 29	10
Example 30	0.1
Example 31	10
Example 32	3
Example 33	0.3
Example 34	0.1
Example 35	0.3
Example 36	10
Example 37	1
Example 38	3
Example 39	0.1
Example 40	3
Example 41	0.01
Example 42	0.003
Example 43	0.1
Example 44	0.1
Example 45	1
Example 46	1
Example 47	1
Example 48	1
Example 49	3
Example 50	1
Example 51	1
Example 52	3
Example 53	3

Table 5: (continued)

Differentiation-inducing action to A2780 cells	
Test Compound	ALPmin (μM)
Example 54	3
Example 55	3
Example 56	3
Example 59	3
Example 60	3
Example 61	3
Example 62	3
Example 63	3
Example 64	3
Example 66	0.1
Example 67	10
Example 68	10
Example 69	3
Example 70	10
Example 72	1
Example 73	3
Example 75	0.1
Example 76	0.1
Example 77	0.3
Example 78	0.1
Example 79	0.3
Example 80	3
Example 81	0.1
Example 82	3
Example 83	3
Example 84	3
Example 85	10
Example 86	0.1
Example 87	0.1
Example 88	3
Example 89	1
Example 90	3
Example 91	3
Example 92	1
Example 93	1
Example 94	1
Example 95	1

Table 5: (continued)

Differentiation-inducing action to A2780 cells	
Test Compound	ALPmin (μM)
Example 96	1
Example 97	3
Example 98	1
Example 99	3
Example 100	3
Example 101	0.1
Example 102	0.3
Example 103	3
Example 104	0.01
Example 105	0.01
Example 108	3
Example 109	0.3
Example 110	3
Example 111	0.03
Example 112	3
Example 113	3
Example 114	0.1
Example 115	3
Example 116	0.3
Example 118	10
Example 119	3
Example 120	3
Example 121	3
Comp.Ex.1	>100
Comp.Ex.2	>100

Pharmacological test example 2

Antitumor test procedure

[0207] Murine myeloid leukemia cells WEHI-3 (1 to 3 × 10^6 cells) were intraperitoneally inoculated to a Balb/C mouse, and administration of a test compound was initiated on the next day. The day was Day 1 and subsequently the drug was orally administered once a day in Day 1 to 4 and in Day 7 to 11. Survival days after inoculation were observed, which were used to calculate the ratio of the survival days for the test coompound group to those for the control group (T/C, %). The ratio was used to evaluate a life prolongation effect.

Results

[0208] The results are shown in Table 6.

Table 6:

Antitumor action to WEHI-3 cells		
Test compound	Dose(μmol/kg)	T/C(%)
Example 42	16	138
Example 43	32	141
Example 44	130	190
Example 117	130	189

Pharmacological test example 3

Antitumor action test

Experimental procedure

[0209] To a nude mouse was inoculated tumor cells subcutaneously subcultured in a nude mouse (HT-29, KB-3-1). When the volume became about 20 to 100 mm^3 and take was confirmed, administration of a drug was initiated. This day was Day 1, and subsequently the drug was orally administered in Day 1 to 5, in Day 8 to 12, Day 15 to 19 and in Day 22 to 26.

[0210] The volume of the tumor was determined from the following equation:

$$(\text{Volume of a tumor}) = 1/2 \times (\text{major axis}) \times (\text{minor axis})^{*2}$$

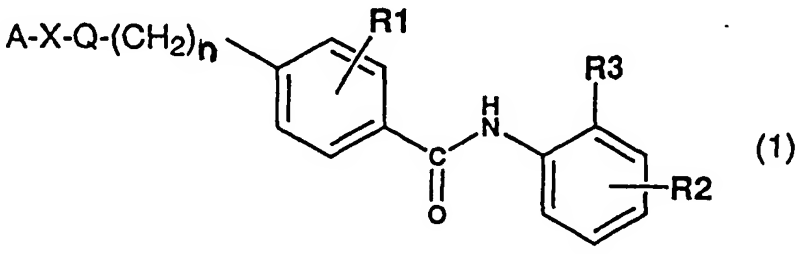
Results

[0211] The results for the compound of Example 44 (dose: 66 μmol/kg) against HT-29 are shown in Figure 1.

[0212] The results for the compound of Example 44 (dose: 66 μmol/kg) against KB-3-1 are shown in Figure 2.

Claims

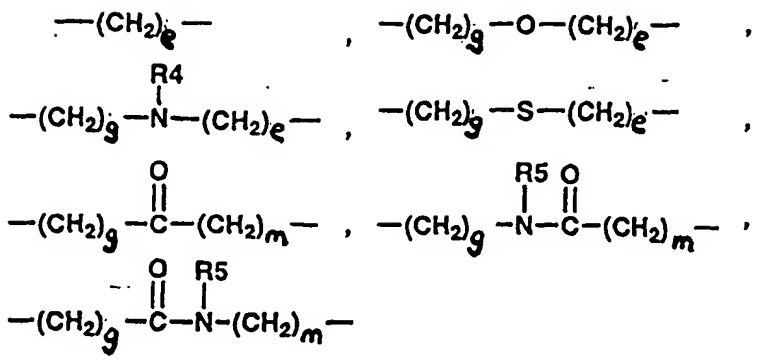
1. A pharmaceutical composition comprising, as active ingredient, one or more compounds represented by formula (1):



(1)

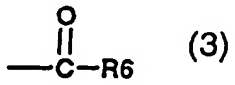
wherein A is an optionally substituted a phenyl or heterocyclic group which has 1 to 4 substituents selected from the group consisting of a halogen atom, a hydroxyl group, an amino group, a nitro group, a cyano group, an alkyl group having 1 to 4 carbons, an alkoxy group having 1 to 4 carbons, an aminoalkyl group having 1 to 4 carbons, an alkylamino group having 1 to 4 carbons, an acyl group having 1 to 4 carbons, an acylamino group having 1 to 4 carbons, an alkylthio group having 1 to 4 carbons, a perfluoroalkyl group having 1 to 4 carbons, a perfluoroalkyloxy group having 1 to 4 carbons, a carboxyl group, an alkoxycarbonyl group having 1 to 4 carbons, a phenyl group and a heterocyclic group;

X is a bond or a moiety having a structure selected from those illustrated in formula (2):



(2)

wherein e is an integer of 1 to 4; g and m are independently an integer of 0 to 4; R^4 is a hydrogen atom or an optionally substituted alkyl group having 1 to 4 carbons, or the acyl group represented by formula (3)

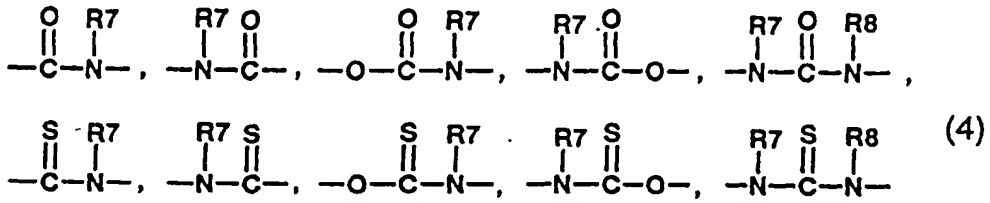


(3)

wherein R^6 is an optionally substituted alkyl group having 1 to 4 carbons, a perfluoroalkyl group having 1 to 4 carbons, a phenyl group or a heterocyclic group; R^5 is a hydrogen atom or an optionally substituted alkyl group having 1 to 4 carbons;

n is an integer of 0 to 4, provided that when X is a bond, n is not zero;

Q is a moiety having a structure selected from those illustrated in formula (4)



(4)

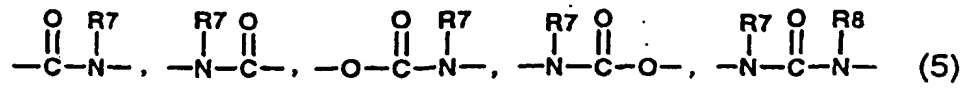
wherein R^7 and R^8 are independently a hydrogen atom or an optionally substituted alkyl group having 1 to 4 carbons;

R^1 and R^2 are independently a hydrogen atom, a halogen atom, a hydroxyl group, an amino group, an alkyl group having 1 to 4 carbons, an alkoxy group having 1 to 4 carbons, an aminoalkyl group having 1 to 4 carbons, an alkylamino group having 1 to 4 carbons, an acyl group having 1 to 4 carbons, an acylamino group having 1 to 4 carbons, an alkylthio group having 1 to 4 carbons, a perfluoroalkyl group having 1 to 4 carbons, a perfluoroalkyloxy group having 1 to 4 carbons, a carboxyl group or an alkoxycarbonyl group having 1 to 4 carbons;

R^3 is an amino group; or a pharmaceutically acceptable salt thereof.

2. A composition as claimed in Claim 1, wherein n is an integer of 1 to 4.

3. A composition as claimed in Claim 1 or 2, wherein Q is selected from the structures illustrated in formula (5):



(5)

wherein R^7 and R^8 are as defined above.

4. A composition as claimed in Claim 1, 2 or 3, wherein A is an optionally substituted hetero ring.

5. A composition as claimed in Claim 4, wherein A is an optionally substituted pyridyl group.

6. A composition as claimed in any preceding Claim wherein X is a direct bond.

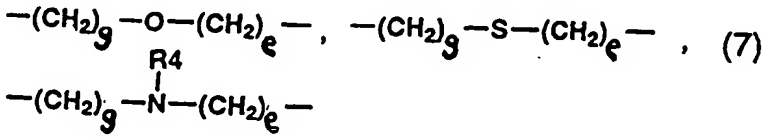
7. A composition as claimed in any preceding Claim, wherein R^1 and R^2 are a hydrogen atom.

8. A composition as claimed in any of Claims 1-5 or 7 wherein X is the structure represented by formula (6):

$$-(CH_2)_e- \quad (6)$$

[wherein e is as defined above.]

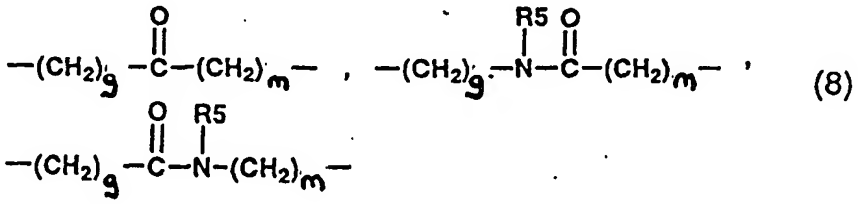
9. A composition as claimed in any of Claims 1-5 or 7 wherein X is selected from the structures illustrated in formula (7):



(7)

[wherein e, g and R^4 are as defined above.]

10. A composition as claimed in any of Claims 1-5 or 7 wherein X is selected from the structures illustrated in formula (8) :



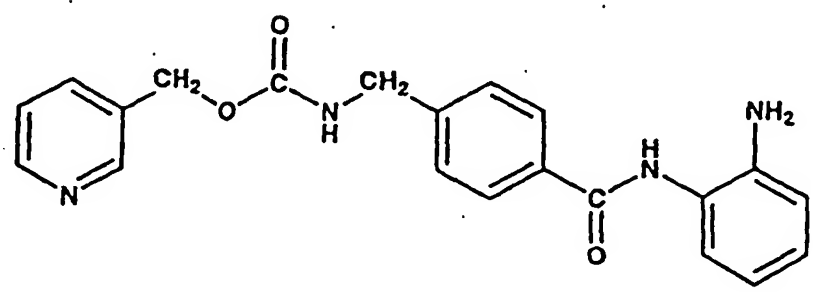
(8)

[wherein g, m and R^5 are as defined above.]

11. A composition as claimed in any preceding Claim, wherein n is 1; and R^1 and R^2 are a hydrogen atom.

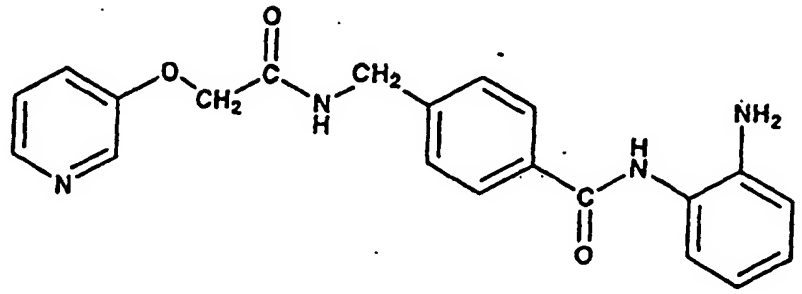
12. A composition as claimed in any of Claims 1, or 3-10 wherein n is zero.

13. A composition as claimed in Claim 1 wherein a said compound is represented by formula (9).



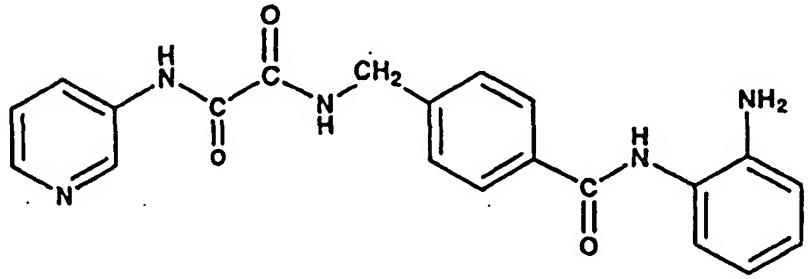
(9)

14. A composition as claimed in Claim 1 wherein a said compound is represented by formula (10).



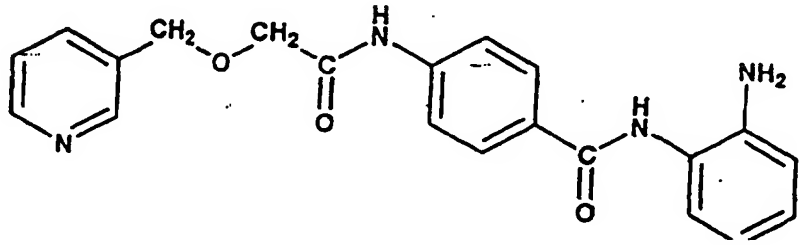
(10)

15. A composition as claimed in Claim 1 wherein a said compound is represented by formula (11).



(11)

16. A composition as claimed in Claim 1 wherein a said compound is represented by formula (12).



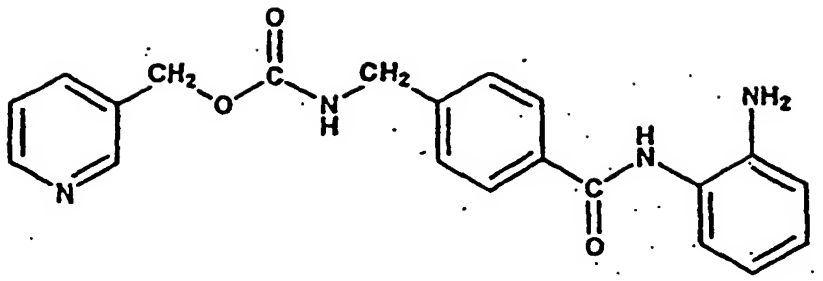
(12)

17. An anticancer drug comprising one or more compounds as defined in any of Claims 1 to 16 as active ingredients.

18. Use of a compound as defined in any of Claims 1-16 in the manufacture of a composition for use in the treatment of cancer.

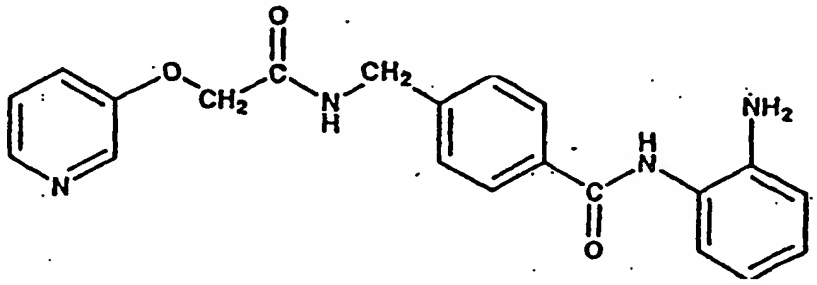
19. A compound represented by Formula (1) as defined in any of claims 1 to 16 or a pharmaceutically acceptable salt thereof.

20. A compound as claimed in claim 19, which is represented by formula (9)



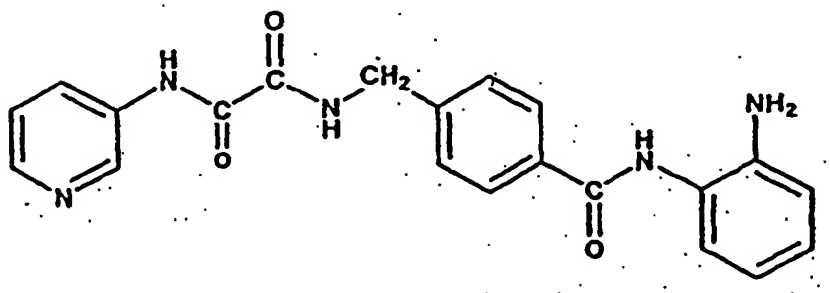
(9)

21. A compound as claimed in claim 19, which is represented by formula (10).



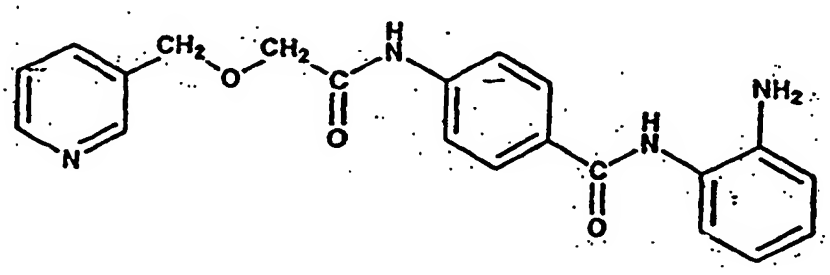
(10)

22. A compound as claimed in claim 19, which is represented by formula (11).



(11)

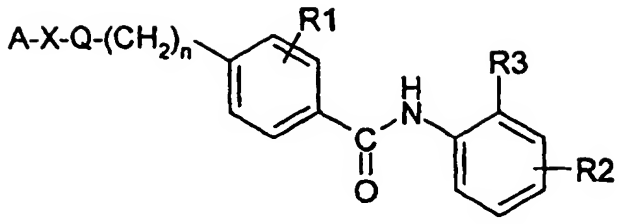
23. A compound as claimed in claim 19, which is represented by formula (12).



(12)

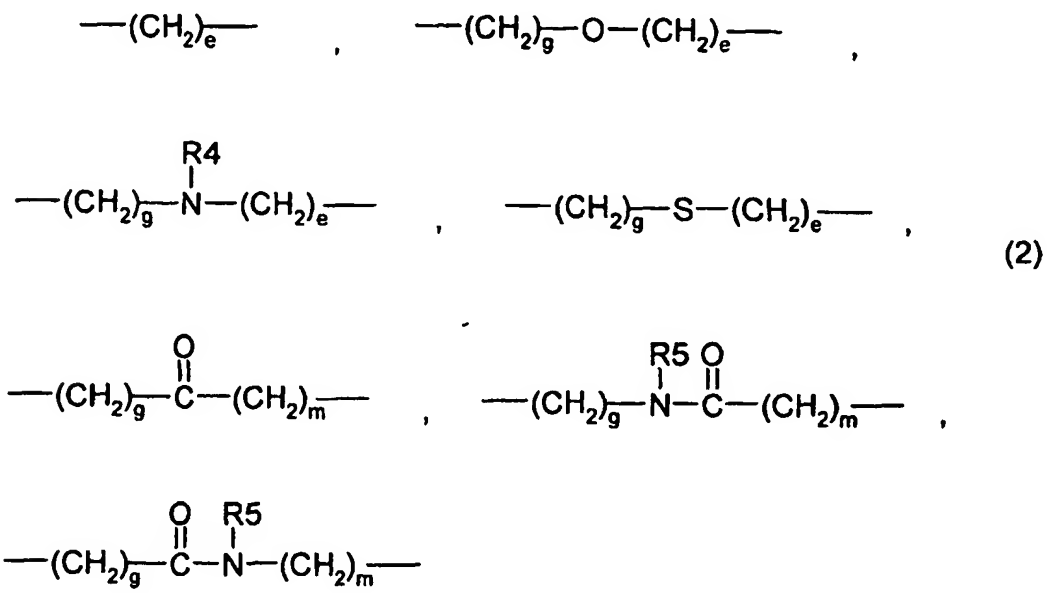
Patentansprüche

1. Pharmazeutische Zusammensetzung, umfassend als aktive Komponente eine oder mehrere Verbindungen dargestellt durch Formel (1):



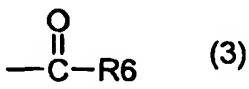
(1)

wobei
A eine gegebenenfalls substituierte Phenyl- oder heterocyclische Gruppe ist, die 1 bis 4 Substituenten aufweist, ausgewählt aus der Gruppe bestehend aus einem Halogenatom, einer Hydroxylgruppe, einer Aminogruppe, einer Nitrogruppe, einer Cyanogruppe, einer Alkylgruppe mit 1 bis 4 Kohlenstoffatomen, einer Alkoxygruppe mit 1 bis 4 Kohlenstoffatomen, einer Aminoalkylgruppe mit 1 bis 4 Kohlenstoffatomen, einer Alkylaminogruppe mit 1 bis 4 Kohlenstoffatomen, einer Acylgruppe mit 1 bis 4 Kohlenstoffatomen, einer Acylaminogruppe mit 1 bis 4 Kohlenstoffatomen, einer Alkylthiogruppe mit 1 bis 4 Kohlenstoffatomen, einer Perfluoroalkylgruppe mit 1 bis 4 Kohlenstoffatomen, einer Perfluoroalkyloxygruppe mit 1 bis 4 Kohlenstoffatomen, einer Carboxylgruppe, einer Alkoxycarbonylgruppe mit 1 bis 4 Kohlenstoffatomen, einer Phenylgruppe und einer heterocyclischen Gruppe;
X eine Bindung oder eine Gruppe mit einer Struktur ist, die aus den in Formel (2) dargestellten Strukturen ausgewählt ist:



(2)

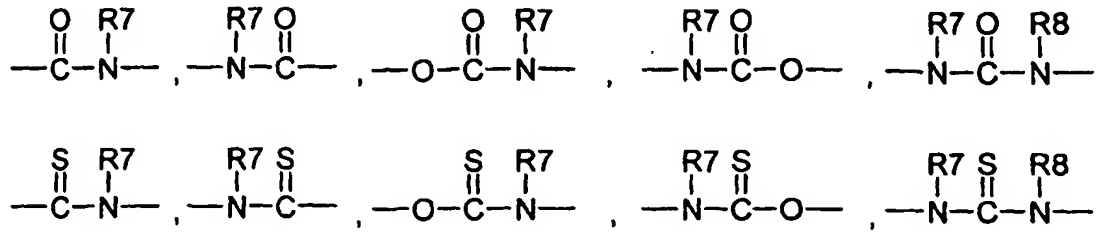
wobei e eine ganze Zahl von 1 bis 4 ist; g und m unabhängig voneinander ganze Zahlen von 0 bis 4 sind; R^4 ein Wasserstoffatom oder eine gegebenenfalls substituierte Alkylgruppe mit 1 bis 4 Kohlenstoffatomen oder die Acylgruppe, wie in Formel (3) dargestellt, ist,



(3)

wobei R^6 eine gegebenenfalls substituierte Alkylgruppe mit 1 bis 4 Kohlenstoffatomen, eine Perfluoralkylgruppe mit 1 bis 4 Kohlenstoffatomen, eine Phenylgruppe oder eine heterocyclische Gruppe ist; R^5 ein Wasserstoffatom oder eine gegebenenfalls substituierte Alkylgruppe mit 1 bis 4 Kohlenstoffatomen ist;
n eine ganze Zahl von 0 bis 4 ist, mit der Bedingung, dass n nicht 0 sein kann, wenn X eine Bindung ist;

Q eine Gruppe mit einer Struktur ist, die aus den in Formel (4) dargestellten Strukturen ausgewählt ist:

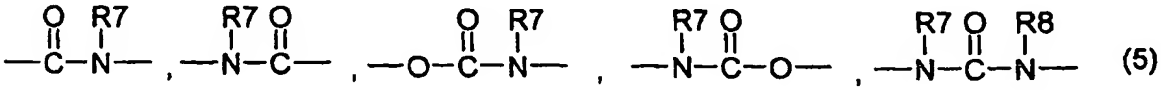


(4)

wobei R^7 und R^8 unabhängig voneinander ein Wasserstoffatom oder eine gegebenenfalls substituierte Alkylgruppe mit 1 bis 4 Kohlenstoffatomen sind;
R^1 und R^2 unabhängig ein Wasserstoffatom, ein Halogenatom, eine Hydroxylgruppe, eine Aminogruppe, eine Alkylgruppe mit 1 bis 4 Kohlenstoffatomen, eine Alkoxygruppe mit 1 bis 4 Kohlenstoffatomen, eine Aminoalkylgruppe mit 1 bis 4 Kohlenstoffatomen, eine Alkylaminogruppe mit 1 bis 4 Kohlenstoffatomen, eine Acylgruppe mit 1 bis 4 Kohlenstoffatomen, eine Acylaminogruppe mit 1 bis 4 Kohlenstoffatomen, eine Alkylthiogruppe mit 1 bis 4 Kohlenstoffatomen, eine Perfluoralkylgruppe mit 1 bis 4 Kohlenstoffatomen, eine Perfluoralkyloxygruppe mit 1 bis 4 Kohlenstoffatomen, eine Carboxylgruppe, eine Alkoxycarbonylgruppe mit 1 bis 4 Kohlenstoffatomen sind; und R^3 eine Aminogruppe ist;
oder ein pharmazeutisch verträgliches Salz davon.

2. Eine Zusammensetzung gemäß Anspruch 1, wobei n eine ganze Zahl von 1 bis 4 ist.

3. Eine Zusammensetzung gemäß Anspruch 1 oder 2, wobei Q ausgewählt ist aus den Strukturen wie in Formel (5) angegeben:



(5)

wobei R^7 und R^8 wie oben definiert sind.

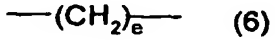
4. Eine Zusammensetzung gemäß Anspruch 1, 2 oder 3, wobei A ein gegebenenfalls substituierter Heteroring ist.

5. Eine Zusammensetzung gemäß Anspruch 4, wobei A eine gegebenenfalls substituierte Pyridylgruppe ist.

6. Eine Zusammensetzung gemäß einem der vorhergehenden Ansprüche, wobei X eine direkte Bindung ist.

7. Eine Zusammensetzung gemäß einem der vorhergehenden Ansprüche, wobei R^1 und R^2 ein Wasserstoffatom sind.

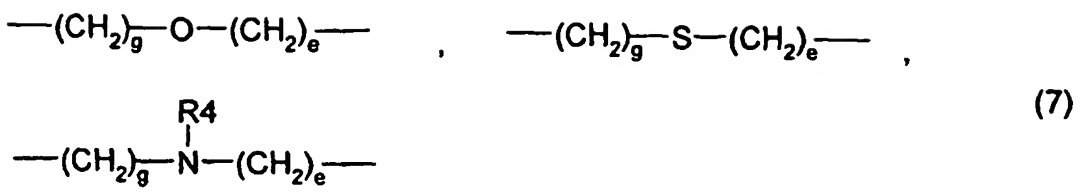
8. Eine Zusammensetzung gemäß einem der Ansprüche 1-5 oder 7, wobei X die in Formel (6) wiedergegebene Struktur ist:



(6)

(wobei e wie oben definiert ist).

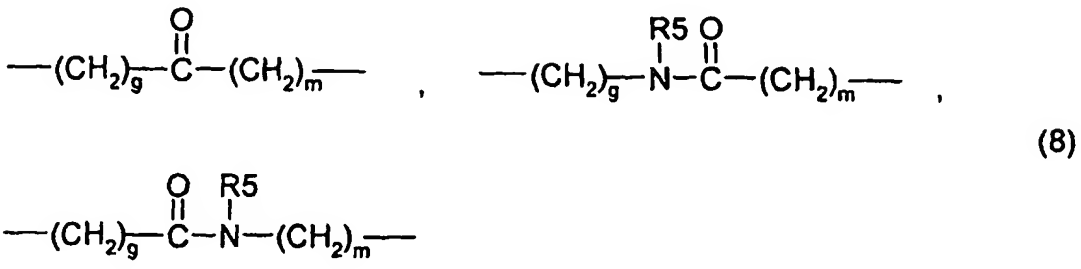
9. Eine Zusammensetzung gemäß einem der Ansprüche 1-5 oder 7, wobei X aus den in Formel (7) wiedergegebenen Strukturen ausgewählt ist: ,



(7)

(wobei e, g und R^4 wie oben definiert sind).

10. Eine Zusammensetzung gemäß einem der Ansprüche 1-5 oder 7, wobei X aus den in Formel (8) wiedergegebenen Strukturen ausgewählt ist:



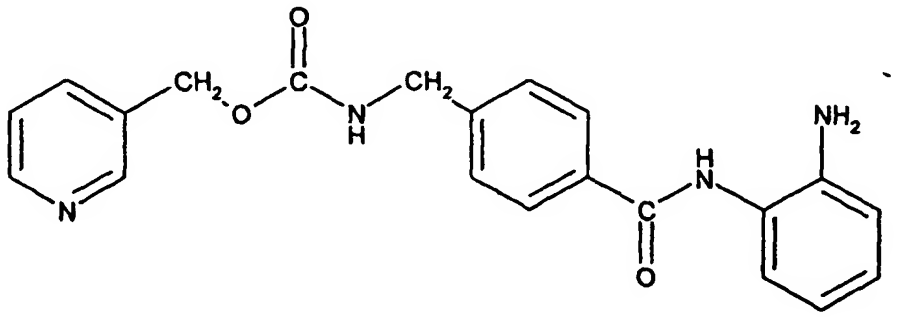
(8)

(wobei g, m und R^5 wie oben definiert sind).

11. Eine Zusammensetzung gemäß einem der vorhergehenden Ansprüche, wobei n gleich 1 ist und R^1 und R^2 ein Wasserstoffatom sind.

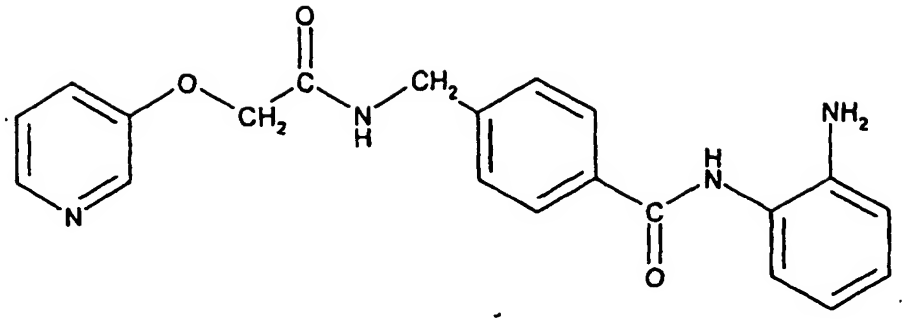
12. Eine Zusammensetzung gemäß einem der Ansprüche 1 oder 3-10, wobei n gleich Null ist.

13. Eine Zusammensetzung gemäß Anspruch 1, wobei die genannte Verbindung durch Formel (9) dargestellt wird:



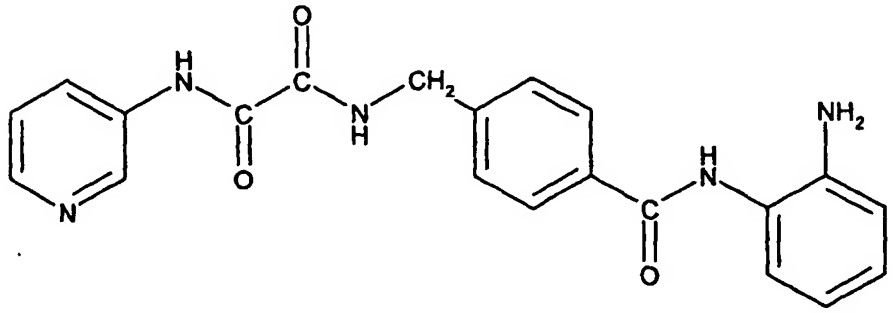
(9)

14. Eine Zusammensetzung gemäß Anspruch 1, wobei die genannte Verbindung durch Formel (10) dargestellt wird:



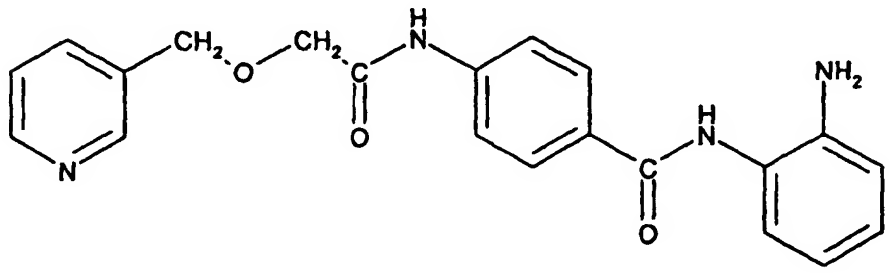
(10)

15. Eine Zusammensetzung gemäß Anspruch 1, wobei die genannte Verbindung durch Formel (11) dargestellt wird:



(11)

16. Eine Zusammensetzung gemäß Anspruch 1, wobei die genannte Verbindung durch Formel (12) dargestellt wird:



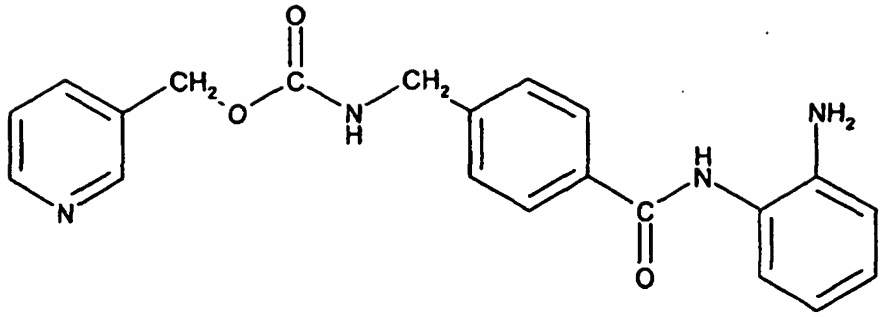
(12)

17. Ein Antikrebsmittel, welches eine oder mehrere Verbindungen wie in einem der Ansprüche 1 bis 16 definiert als aktive Bestandteile umfasst.

18. Verwendung einer Verbindung wie in einem der Ansprüche 1-16 definiert zur Herstellung einer Zusammensetzung zur Verwendung in der Behandlung von Krebs.

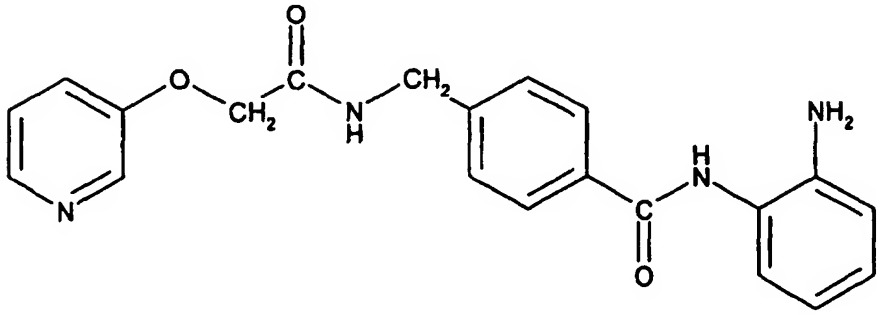
19. Eine durch Formel (1) dargestellte Verbindung wie in einem der Ansprüche 1-16 definiert, oder ein pharmazeutisch verträgliches Salz davon.

20. Eine Verbindung gemäß Anspruch 19, die durch Formel (9) dargestellt wird:



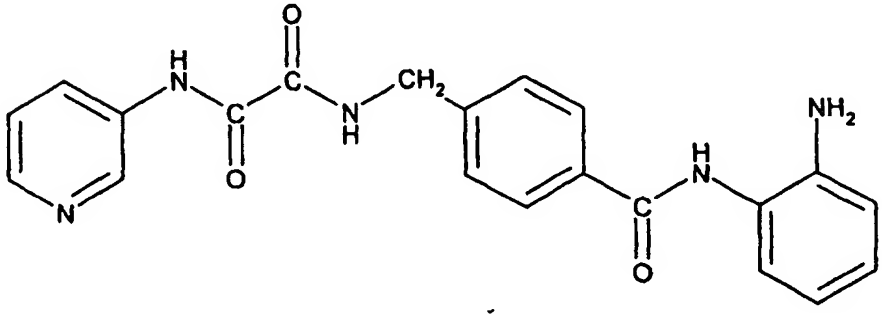
(9)

21. Eine Verbindung gemäß Anspruch 19, die durch Formel (10) dargestellt wird:



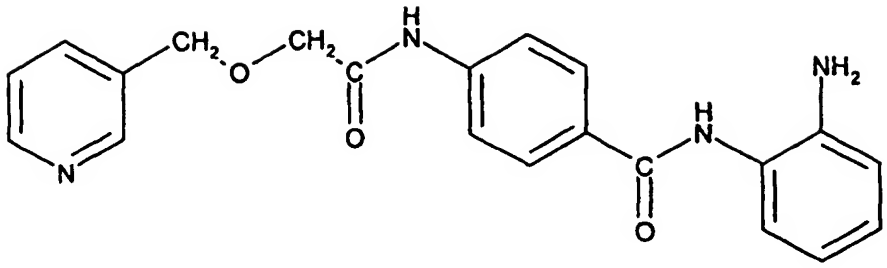
(10)

22. Eine Verbindung gemäß Anspruch 19, die durch Formel (11) dargestellt wird:



(11)

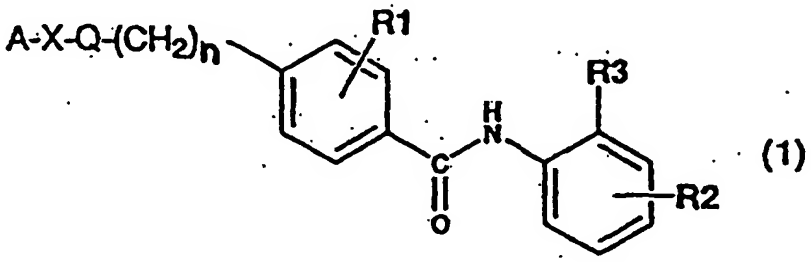
23. Eine Verbindung gemäß Anspruch 19, die durch Formel (12) dargestellt wird:



(12)

Revendications

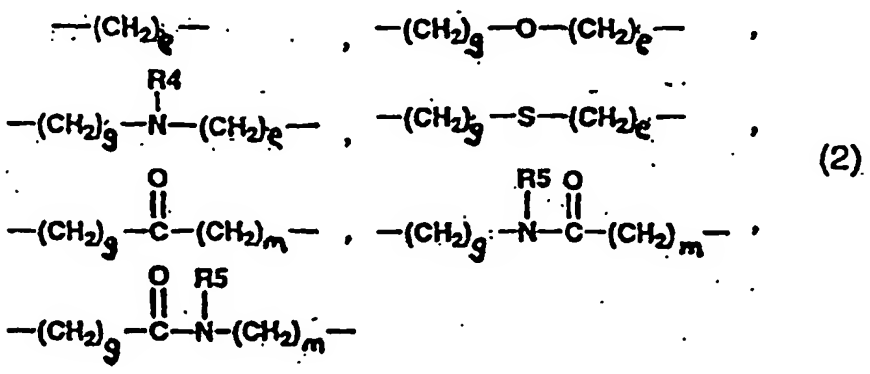
1. Composition pharmaceutique comprenant, en tant qu'ingrédient actif, un ou plusieurs composés de formule (1) :



(1)

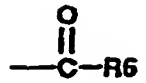
où A représente un groupe phényle ou hétérocyclique facultativement substitué présentant 1 à 4 substituants pris dans le groupe comprenant un atome d'halogène, un groupe hydroxyle, un groupe amino, un groupe nitro, un groupe cyano, un groupe alkyle présentant 1 à 4 atomes de carbone, un groupe alkoxy présentant 1 à 4 atomes de carbone, un groupe aminoalkyle présentant 1 à 4 atomes de carbone, un groupe alkylamino présentant 1 à 4 atomes de carbone, un groupe acyle présentant 1 à 4 atomes de carbone, un groupe acylamino présentant 1 à 4 atomes de carbone, un groupe alkylthio présentant 1 à 4 atomes de carbone, un groupe perfluoroalkyle présentant 1 à 4 atomes de carbone, un groupe perfluoroalkyloxy présentant 1 à 4 atomes de carbone, un groupe carboxyle, un groupe alkoxycarbonyle présentant 1 à 4 atomes de carbone, un groupe phényle et un groupe hétérocyclique ;

X représente une liaison ou un fragment de structure pris parmi ceux illustrés par la formule (2) :



(2)

où e est un entier de 1 à 4 ; g et m sont indépendamment l'un de l'autre un entier de 0 à 4 ; R^4 représente un atome d'hydrogène ou un groupe alkyle facultativement substitué présentant 1 à 4 atomes de carbone, ou le groupe acyle est représenté par la formule (3)

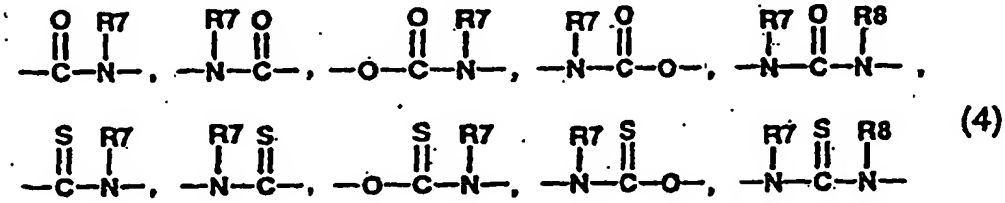


(3)

où R^6 représente un groupe alkyle facultativement substitué présentant 1 à 4 atomes de carbone, un groupe perfluoroalkyle présentant 1 à 4 atomes de carbone, un groupe phényle ou. un groupe hétérocyclique ; R^5 représente un atome d'hydrogène ou un groupe alkyle facultativement substitué présentant 1 à 4 atomes de carbone ;

n est un entier de 0 à 4, à condition que lorsque X est une liaison, n ne vaille pas zéro ;

Q est un fragment d'une structure prise parmi celles illustrées à la formule (4)



(4)

où R^7 et R^8 indépendamment l'un de l'autre représentent un atome d'hydrogène ou un groupe alkyle facultativement substitué présentant 1 à 4 atomes de carbone ;

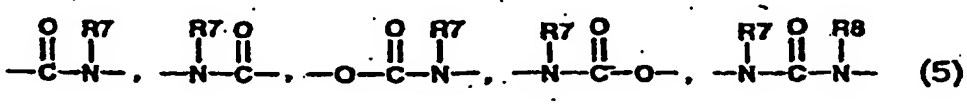
R^1 et R^2 indépendamment l'un de l'autre représentent un atome d'hydrogène, un atome d'halogène, un groupe hydroxyle, un groupe amino, un groupe alkyle présentant 1 à 4 atomes de carbone, un groupe alkoxy présentant 1 à 4 atomes de carbone, un groupe aminoalkyle présentant 1 à 4 atomes de carbone, un groupe alkylamino présentant 1 à 4 atomes de carbone, un groupe acyle présentant 1 à 4 atomes de carbone, un groupe acylamino présentant 1 à 4 atomes de carbone, un groupe alkylthio présentant 1 à 4 atomes de carbone, un groupe perfluoroalkyle présentant 1 à 4 atomes de carbone, un groupe perfluoroalkyloxy présentant 1 à 4 atomes de carbone, un groupe carboxyle ou un groupe alkoxycarbonyle présentant 1 à 4 atomes de carbone ;

R^3 représente un groupe amino ;

ou un sel de celui-ci acceptable en pharmacie.

2. Composition selon la revendication 1, où n est un entier de 1 à 4.

3. Composition selon la revendication 1 ou 2, où Q est pris parmi les structures illustrées par la formule (5) :



(5)

où R^7 et R^8 sont définis comme ci-dessus.

4. Composition selon la revendication 1, 2 ou 3, où A est un hétérocycle facultativement substitué.

5. Composition selon la revendication 4, où A est un groupe pyridyle facultativement substitué.

6. Composition selon l'une quelconque des revendications précédentes, où X est une liaison directe.

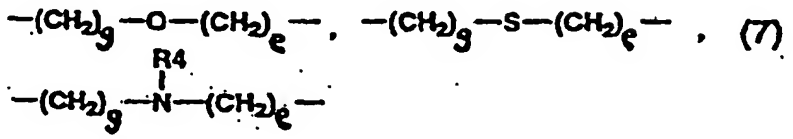
7. Composition selon l'une quelconque des revendications précédentes, où R^1 et R^2 représentent un atome d'hydrogène.

8. Composition selon l'une quelconque des revendications 1 à 5 ou 7, où X répond à la structure représentée par la formule (6) :

$$-(CH_2)_e- \quad (6)$$

[où e est défini comme ci-dessus].

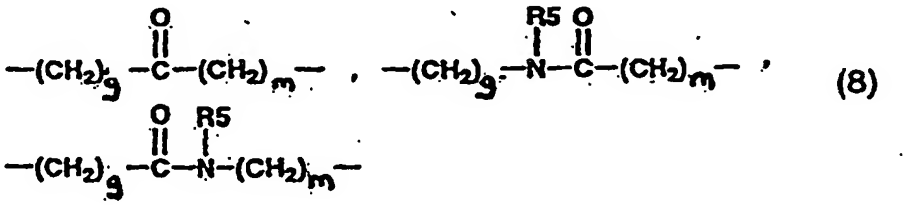
9. Composition selon l'une quelconque des revendications 1 à 5 ou 7, où X est pris parmi les structures illustrées par la formule (7) :



(7)

[où e, g et R^4 sont définis comme ci-dessus].

10. Composition selon l'une quelconque des revendications 1 à 5 ou 7, où X est pris parmi les structures illustrées par la formule (8) :



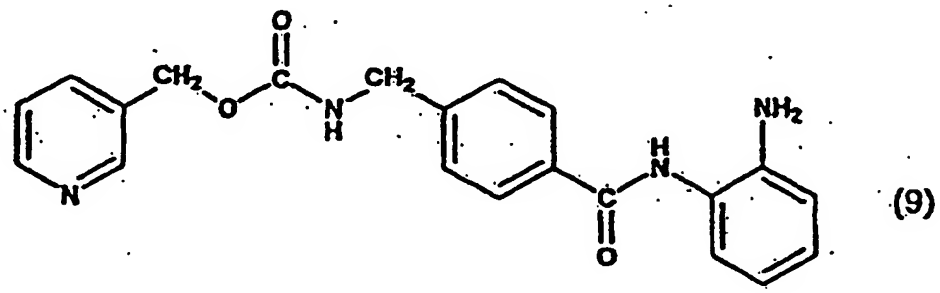
(8)

[où g, m et R^5 sont définis comme ci-dessus].

11. Composition selon l'une quelconque des revendications précédentes, où n vaut 1 ; et R^1 et R^2 représentent un atome d'hydrogène.

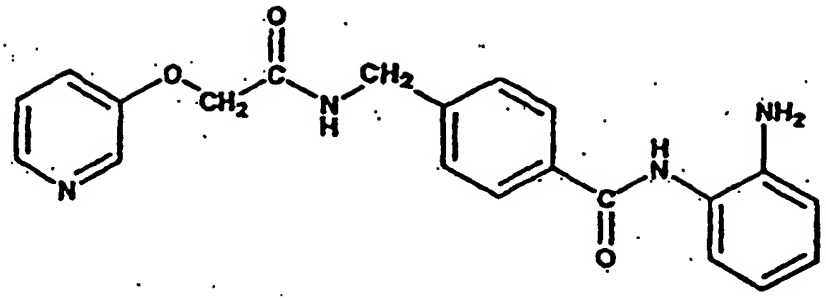
12. Composition selon l'une quelconque des revendications 1, ou 3 à 10, où n vaut zéro.

13. Composition selon la revendication 1, où ledit composé est représenté par la formule (9) :



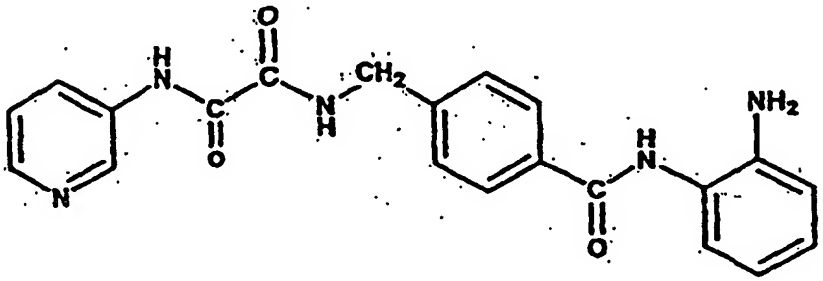
(9)

14. Composition selon la revendication 1, où ledit composé est représenté par la formule (10) :



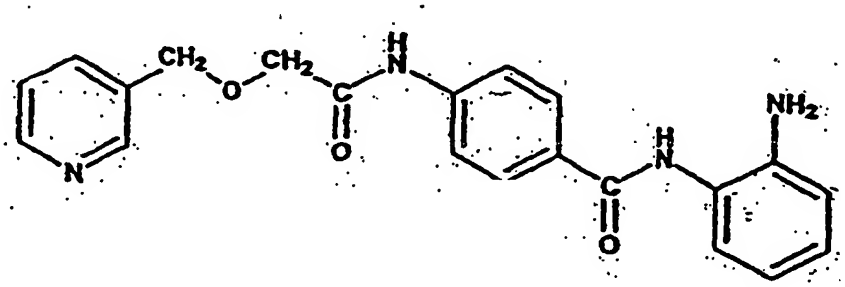
(10)

15. Composition selon la revendication 1, où ledit composé est représenté par la formule (11) :



(11)

16. Composition selon la revendication 1, où ledit composé est représenté par la formule (12) :



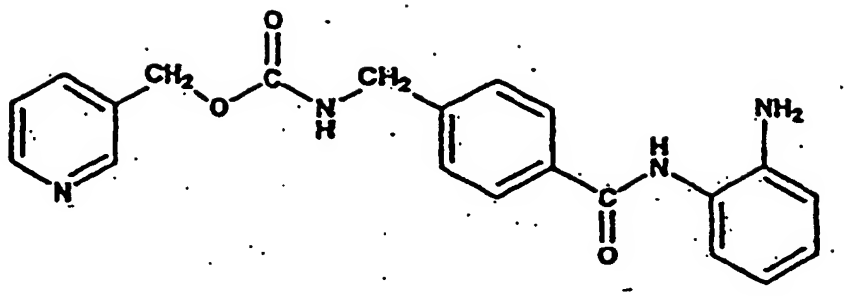
(12)

17. Médicament anticancéreux comprenant un ou plusieurs composés tels que définis selon l'une quelconque des revendications 1 à 16 en tant qu'ingrédients actifs.

18. Utilisation d'un composé tel que défini selon l'une quelconque des revendications 1 à 16 pour la fabrication d'une composition pour l'utilisation dans le traitement du cancer.

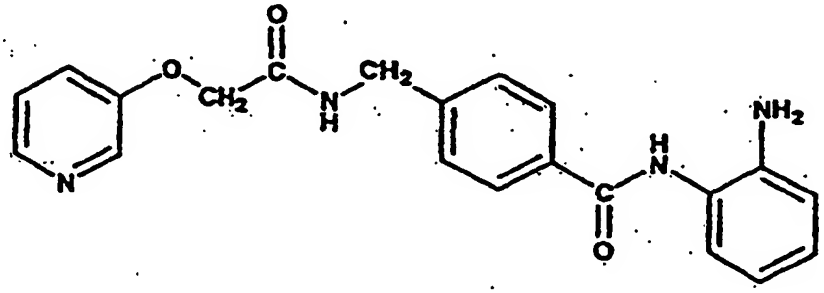
19. Composé représenté par la formule (1) comme défini dans l'une quelconque des revendications 1 à 16 ou un sel de celui-ci acceptable en pharmacie.

20. Composé selon la revendication 19, qui est représenté par la formule (9) :



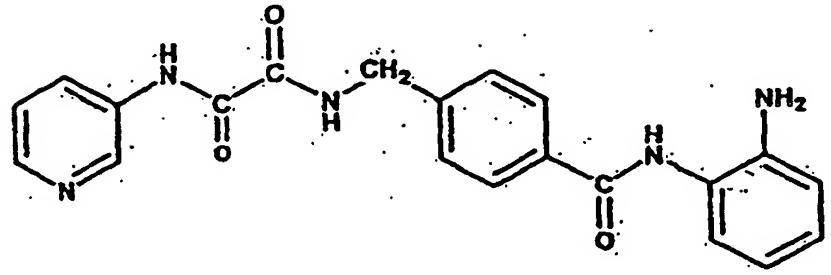
(9)

21. Composé selon la revendication 19, qui est représenté par la formule (10) :



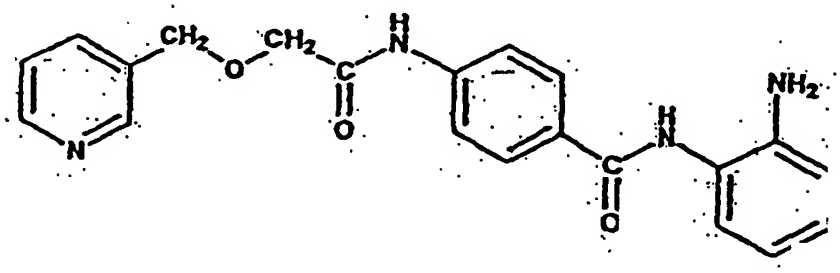
(10)

22. Composé selon la revendication 19, qui est représenté par la formule (11) :



(11)

23. Composé selon la revendication 19, qui est représenté par la formule (12) :



(12)

FIG.1

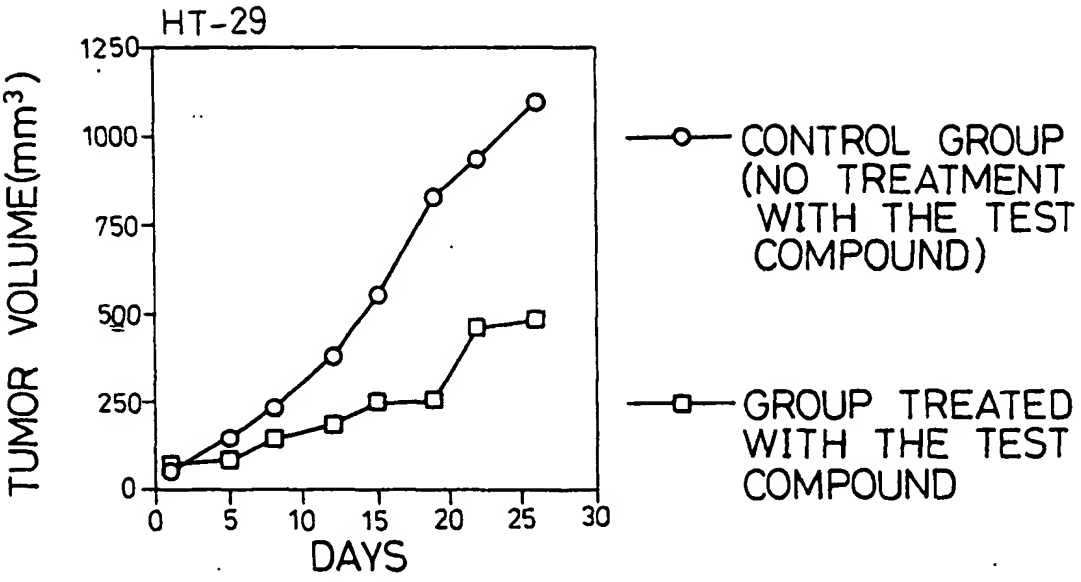
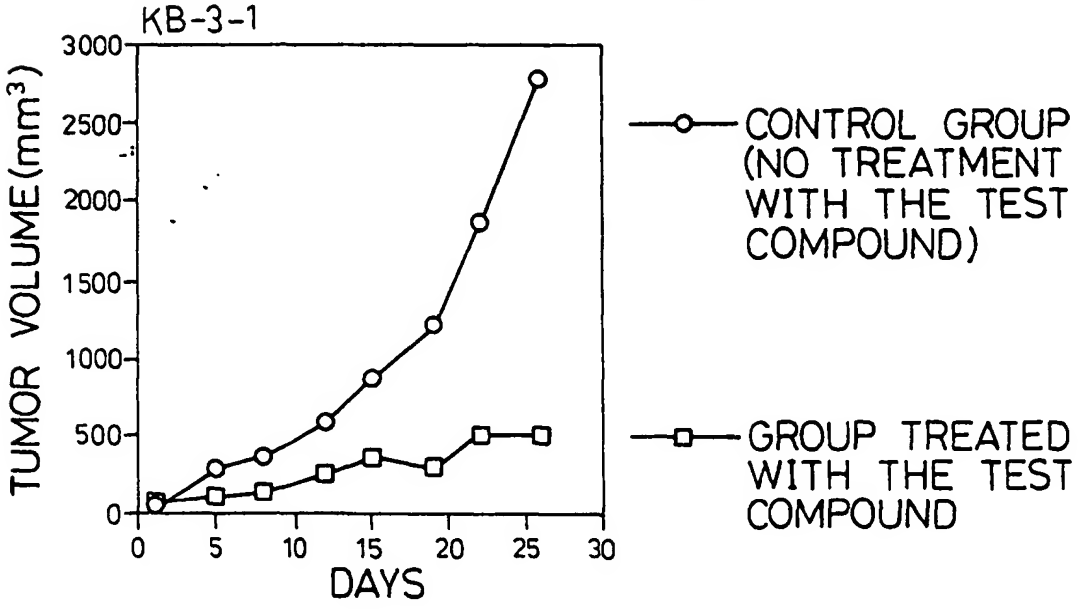

HT-29
TUMOR VOLUME(mm³)
1250
1000
750
500
250
0
0
5
10
15
20
25
30
DAYS
CONTROL GROUP (NO TREATMENT WITH THE TEST COMPOUND)
GROUP TREATED WITH THE TEST COMPOUND

FIG.2


KB-3-1
TUMOR VOLUME(mm³)
3000
2500
2000
1500
1000
500
0
0
5
10
15
20
25
30
DAYS
CONTROL GROUP (NO TREATMENT WITH THE TEST COMPOUND)
GROUP TREATED WITH THE TEST COMPOUND